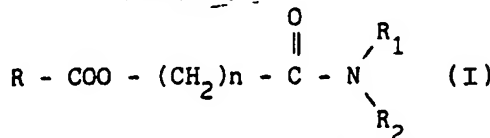
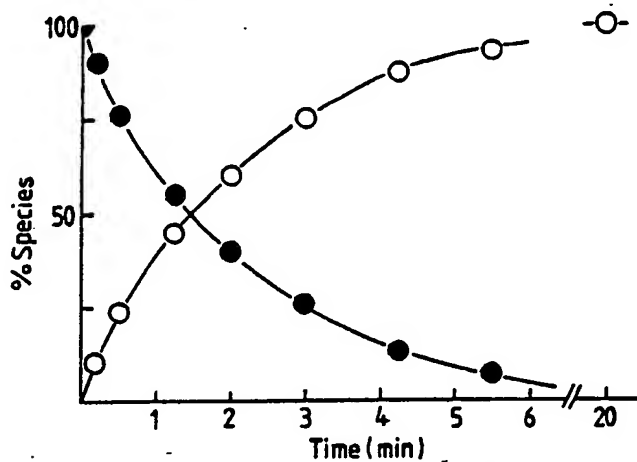




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(54) Title: PRODRUG DERIVATIVES OF CARBOXYLIC ACID DRUGS



(57) Abstract

Novel ester derivatives of carboxylic acid medicaments of formula (I), wherein R-COO - represents the acyloxy residue of a carboxylic acid drug or medicament, n is an integer from 1 to 3, and R₁ and R₂ are the same or different and are selected from a group consisting of an alkyl, an alkenyl, an aryl, an aralkyl, a cycloalkyl and which group may be unsubstituted or substituted, or R₁ and R₂ together with the N forms a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur and which heterocyclic group may be substituted. These compounds are highly biolabile prodrug forms of the corresponding carboxylic acid compounds and are highly susceptible to undergoing enzymatic hydrolysis *in vivo* whereas they are highly stable in aqueous solution. The novel derivatives are less irritating to mucosa than the parent carboxylic acids and may provide an improved bioavailability of the drugs.

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PRODRUG DERIVATIVES OF CARBOXYLIC ACID DRUGS

BACKGROUND OF THE INVENTION

5 Field of the invention

The present invention relates to novel highly biolabile prodrug forms of drugs containing one or more carboxylic acid functions, to methods for preparing the prodrug forms, to pharmaceutical compositions containing such prodrug forms, and to methods for using the prodrug forms.

For purposes of this specification, the term "prodrug" denotes a derivative of a known and proven carboxylic acid functional drug (e.g. naproxen, L-dopa, salicylic acid, etc.) which derivative, when administered to warm-blooded animals, e.g. humans, is converted into the proven drug. The enzymatic and/or chemical hydrolytic cleavage of the compounds of the present invention occurs in such a manner that the proven drug form (parent carboxylic acid drug) is released, and the moiety or moieties split off remain nontoxic or are metabolized so that nontoxic metabolic products are produced.

These novel prodrug forms are esters of certain hydroxy-amides. These esters combine a high susceptibility to undergo enzymatic hydrolysis in vivo with a high stability in aqueous solution. The new ester prodrug type is further characterized by providing ample possibilities for varying the aqueous solubility as well as the lipophilicity of the prodrug derivatives with retainment of a favourable enzymatic/-non-enzymatic hydrolysis index.

30 Description of the prior art

It is well-known that a wide variety of compounds containing carboxylic acid functions are biologically active. For example, such structure is characteristic of non-steroidal anti-inflammatory agents such as naproxen, ibuprofen, indomethacin and the like; penicillin and cephalosporin antibiotics such as ampicillin, cefmetazole and the

like; as well as other compounds having diverse biological properties and structures.

5 It is also well-known that such prior art compounds are characterized by certain inherent disadvantages, notably bioavailability problems upon administration via oral, rectal or topical routes. The unionized form of a drug is usually absorbed more efficiently than its ionic species and as the carboxylic acid functional group is significantly ionized at physiological pH, the result is that carboxylic acid 10 agents are poorly absorbed through lipid-water membrane barriers. In addition, by suffering from reduced bioavailability, some acidic drugs, notably non-steroidal anti-inflammatory agents (ibuprofen, tolmetin, naproxen, indomethacin, etc.), are irritating to the mucous membrane of the gastro-intestinal tract.

15 A promising approach to solve such problems may be esterification of the carboxylic acid function to produce lipophilic and non-irritating prodrug forms, provided that the biologically active parent drug can be released from the prodrug form at its sites of activity. However, several aliphatic or aromatic esters of carboxylic acid drugs are not 20 sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. For example, simple alkyl and aryl esters of penicillins are not hydrolyzed to active free penicillin acid in vivo (Holysz & Stavely, 1950) and therefore have no therapeutic potential (Ferres, 1983). Similarly, the much reduced 25 anti-inflammatory activity observed for the methyl or ethyl esters of naproxen (Harrison et al., 1970) and fenbufen (Child et al., 1977) relative to the free acids may be ascribed to the resistance of the esters to be hydrolyzed in vivo. In the field of angiotensin-converting enzyme inhibitors ethyl esters have been developed as pro- 30 drugs for the parent active carboxylic acid drugs in order to improve their oral bioavailability. Enalapril is such a clinically used ethyl ester prodrug of enalaprilic acid. Plasma enzymes do not hydrolyze the ester and the necessary conversion of the ester to the free acid predominantly takes place in the liver (Tocco et al., 1982; Larmour 35 et al., 1985). As recently suggested (Larmour et al., 1985), liver

function may thus be a very important determinant for the bioactivation of enalapril and hence its therapeutic effect. The limited susceptibility of enalapril to undergo enzymatic hydrolysis in vivo has been shown to result in incomplete availability of the active parent acid (Todd & Heel, 1986). Pentopril is another ethyl ester prodrug of an angiotensin-converting enzyme inhibitor which also is highly stable in human plasma. In this case less than 50% of an oral dose of the prodrug ester appears to be deesterified in vivo to the active parent acid (Rakhit & Tipnis, 1984; Tipnis & Rakhit, 1985).

As has been demonstrated in the case of penicillins (Ferres, 1983) these shortcomings of some ester prodrugs may be overcome by preparing a double ester type, acyloxyalkyl or alkoxycarbonyloxyalkyl esters, which in general show a higher enzymatic lability than simple alkyl esters. The general utility of this double ester concept in prodrug design is, however, limited by the poor water solubility of the esters of several drugs and the limited stability of the esters in vitro. In addition, such esters are oils in many cases, thus creating pharmaceutical formulation problems.

In view of the foregoing, it is quite obvious that a clear need exists for new ester prodrug types possessing a high susceptibility to undergo enzymatic hydrolysis in plasma or blood and furthermore being characterized by providing ample possibilities for varying or controlling the water and lipid solubilities.

In accordance with the present invention it has now been discovered that esters of the formula I below are surprisingly rapidly cleaved enzymatically in vivo, e.g. by plasma enzymes, and fulfil the above-discussed desirable attributes.

A few compounds related to certain compounds of formula I have been reported in the literature. Thus, Boltze et al. (1980) have described various N-unsubstituted and N-monosubstituted 2-[1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyloxy]-acetamide derivatives having anti-inflammatory properties. Similarly, some acetamide derivatives of flufenamic acid have been reported by Boltze & Kreisfeld (1977). 2-[2-(Acetyloxy)benzoyloxy]-acetamide and other related

ester derivatives of acetylsalicylic acid are disclosed in Ger. Offen. 2,320,945.

5 However, there is no suggestion that the compounds described have any prodrug activity, and enzymatic hydrolysis of the compounds into the parent carboxylic acid drugs is neither explicitly nor implicitly mentioned.

SUMMARY OF THE INVENTION

10 It is an object of the present invention to provide a novel ester prodrug type characterized by possessing a high susceptibility to undergo enzymatic hydrolysis in vivo and at the same time providing ample possibilities for varying the water and lipid solubilities of the derivatives.

15 It is another object of the present invention to provide novel bio-reversible derivatives for drugs or biologically active agents having a carboxylic acid function which derivatives, when administered to warm-blooded animals, e.g. humans, elicit the bio-affecting/pharmacological response characteristic of the acids from which they are derived, yet which are characterized in being less irritating to
20 topical and gastric or intestinal mucosal membranes.

It is another object of this invention to provide prodrugs of carboxylic acid agents which are capable of providing increased bio-
25 membrane transport so that the parent drugs are more bioavailable from the site of administration such as the gastro-intestinal tract, the rectum, the skin or the eye of the human body.

It is a further object of the present invention to provide such
30 derivatives of conventional carboxylic acids which are prodrugs designed to cleave in such a manner as to enable the original parent drug form to be released at its therapeutic site or sites of activity, while the remaining cleaved moiety is non-toxic and/or is metabolized in a nontoxic fashion.

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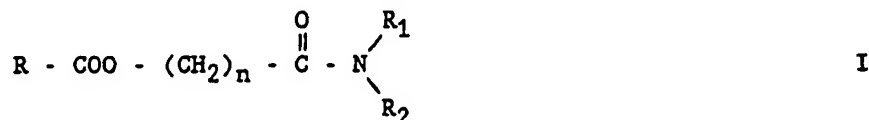
It is still another object of this invention to provide prodrug compounds which utilize hydrolytic enzymes to generate the parent carboxylic acid-type drug from the prodrug form.

5 It is yet another object of the present invention to provide derivatives of carboxylic acid agents which derivatives are "soft" in nature, i.e., which are characterized by in vivo destruction to essentially non-toxic moieties, after they have achieved their desired therapeutic role (for example, the compounds derived from steroidal
10 acids of formula II below).

Other objects, features and advantages of the invention will be apparent to those skilled in the art from the detailed description of the invention which follows.

15 The foregoing objects, features and advantages are provided by the novel compounds of the formula I

20



25

wherein R-COO- represents the acyloxy residue of a carboxylic acid drug or medicament,

30 n is an integer from 1 to 3, and

R₁ and R₂ are the same or different and are selected from a group consisting of an alkyl group, an alkenyl group, an aryl group, an aralkyl group, a cycloalkyl group, in which the alkyl, alkenyl, aryl, aralkyl or cycloalkyl group is unsubstituted or substituted with one
35 or more substituents selected from:

- a halogen atom,
- a hydroxy group,
- a carbonyl group,
- 5 - a straight or branched-chain alkoxy group having the formula R_3-O- , wherein R_3 represents an alkyl group or an aryl group, which groups may be unsubstituted or substituted with one or more of a halogen atom or a hydroxy group,
- a carbamoyl group having the formula $-\text{CON} \begin{smallmatrix} R_5 \\ R_4 \end{smallmatrix}$,
- 10 wherein R_4 and R_5 are the same or different and are hydrogen, an alkyl group or are selected from a group having the formula $-\text{CH}_2\text{NR}_7\text{R}_6$, wherein R_6 and R_7 are the same or different and are hydrogen, an alkyl group, or together with the adjacent nitrogen atom form a 4-, 5-, 6- or 7-membered heterocyclic ring,
- 15 which in addition to the nitrogen may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
- an amino group having the formula $-\text{NR}_8\text{R}_9$, wherein R_8 and R_9 are
- 20 the same or different and are hydrogen, an alkyl group or together with the adjacent nitrogen atom form a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,
- 25 - an acyloxy group having the formula $-\text{COOR}_{10}$, wherein R_{10} is an alkyl, aryl or aralkyl group,
- an oxyacyl group having the formula $\text{R}_{11}\text{COO}-$ wherein R_{11} is
- 30 hydrogen, an alkyl group, an aryl group, an aralkyl group, a cycloalkyl group, in which the alkyl, aryl, aralkyl or cycloalkyl group is unsubstituted or substituted with one or more of a halogen atom, a hydroxy group, an alkoxy group of the formula R_3-O- as defined above, a carbamoyl group of the formula $-\text{CONR}_4\text{R}_5$ as defined above or an amino group having the formula
- 35 $-\text{NR}_8\text{R}_9$ as defined above;

or R_1 and R_2 are combined so that $-NR_1R_2$ forms a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and which heterocyclic ring may be substituted with a hydroxy group, a carbonyl group, an alkyl group or an oxyacyl group having the formula $R_{11}COO-$, wherein R_{11} is as defined above, or an acyloxy group having the formula $-COOR_{10}$, wherein R_{10} is as defined above;

and nontoxic pharmaceutically acceptable acid addition salts thereof, with the proviso that if $R_1 = \text{alkyl}$ then $R_2 = \text{alkyl}$, and if $R_1 = CH_2CH_2OH$ then $R_2 = CH_2CH_2OH$.

In the present context, the term "alkyl" designates C_{1-8} alkyl which may be straight or branched, such as methyl, ethyl, propyl, isopropyl, butyl, tert.butyl, pentyl, hexyl, heptyl, or octyl. The term "alkenyl" designates a C_{2-6} -monounsaturated aliphatic hydrocarbon group which may be straight or branched, such as propenyl, butenyl or pentenyl. The term "aryl" encompasses aryl radicals such as phenyl and naphthyl and also the corresponding aryl radicals containing one or more substituents, which may be the same or different, such as alkylthio, alkyl, halogen, alkoxy, nitro, alkanoyl, carbalkoxy, dialkylamino, alkanoyloxy or hydroxy groups. The term "cycloalkyl" designates a radical containing 4 to 7 carbon atoms, e.g. cyclohexyl. The term "aralkyl" designates a radical of the type -alkylene-aryl, wherein aryl is as defined above and the alkylene moiety contains 1 to 6 carbon atoms and can be straight or branched-chain, e.g. methylene, 1,2-butylene, and the like. When R_1 and R_2 in the formula I, R_4 and R_5 in the formula $-CONR_4R_5$ and R_8 and R_9 in the formula $-NR_8R_9$ together with the adjacent nitrogen atom form a 4-, 5-, 6- or 7-membered heterocyclic ring which in addition to the nitrogen atom may contain 1 or 2 further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, it may, for instance, be 1-piperidinyl, 1-pyrrolidinyl, 1-piperazinyl, 4-methyl-1-piperazinyl, hexamethyleneimino, morpholinyl, thiomorpholinyl, 1-pyrazolyl and 1-imidazolyl.

When one or more asymmetric carbon atoms are present in the R_1 or R_2 groups as defined above, it is understood that the present invention also encompasses all diastereomers or enantiomers, or mixtures thereof. Examples of isomers are D-, L-, and DL- forms.

5 The term "non-toxic pharmaceutically acceptable acid addition salts" as used herein generally includes the non-toxic acid addition salts of compounds of formula I, formed with non-toxic inorganic or organic acids. For example, the salts include those derived from inorganic
10 acids such as hydrochloric, hydrobromic, sulphuric, sulphamic, nitric, phosphoric and the like; and the salts with organic acids such as acetic, propionic, succinic, fumaric, maleic, tartaric, citric, glycolic, lactic, stearic, malic, pamoic, ascorbic, phenylacetic, benzoic, glutamic, salicylic, sulphuric, sulphanilic, and
15 the like.

As stated above, $R-COO^-$ in formula I can represent the acyloxy residue of any drug, pharmaceutical or medicament ($R - COOH$) having one or more carboxylic acid functions. The chemical structure of the carboxylic acid agents is not critical. Examples of drugs or pharmaceuticals from which the instant prodrugs are derived include but
20 are not limited to:

a. Non-steroidal anti-inflammatory agents like:

- 25 1. Acetylsalicylic acid (aspirin)
2. Salicylic acid
3. Sulindac
4. Indomethacin
5. Naproxen
30 6. Fenoprofen
7. Ibuprofen
8. Ketoprofen
9. Indoprofen
10. Furobufen
35 11. Diflunisal
12. Tolmetin
13. Flurbiprofen

14. Diclofenac
15. Mefenamic acid
16. Flufenamic acid.
17. Meclofenamic acid
- 5 18. Fenclozic acid
19. Alclofenac
20. Bucloxic acid
21. Suprofen
22. Fluprofen
- 10 23. Cinchophen
24. Pirprofen
25. Oxoprozin
26. Cinmetacin
27. Acemetacin
- 15 28. Ketorolac
29. Clometacin
30. Ibufenac .
31. Tolfenamic acid .
32. Fenclofenac
- 20 33. Prodolic acid
34. Clonixin
35. Flutiazin
36. Flufenisal
37. Salicylsalicylic acid
- 25 38. O-(Carbamoylphenoxy)acetic acid
39. Zomepirac
40. Nifluminic acid
41. Lonazolac
42. Fenbufen
- 30 43. Carprofen
44. Tiaprofenic acid
45. Loxoprofen
46. Etodolac
47. Alminoprofen
- 35 48. 2-(8-Methyl-10,11-dihydro-11-oxodibenz[b,f]oxepin-2-yl)-
propionic acid
49. 4-Biphenylacetic acid

b. Cephalosporin antibiotics like:

- 5 100. Cephalothin
 101. Cephacetrile
 102. Cephapirin
 103. Cephaloridine
 104. Cefazolin
 105. Cefazuflur
 106. Ceforanide
10 107. Cefazedone
 108. Ceftezole
 109. Cephanone
 110. Cefotiam
 111. Cefamandole
15 112. Cefonicid
 113. Cefuroxime
 114. Cefoperazone
 115. Cefpiramide
 116. Cefpimizole
20 117. Cefsulodin
 118. Cefoxitin
 119. Cefmetazole
 120. Cefotetan
 121. Cefbuperazone
25 122. Cefotaxime
 123. Cefmenoxime
 124. Ceftizoxime
 125. Cefpirome
 126. Ceftazidime
30 127. Cefodizime
 128. Ceftriaxone
 129. Latamoxef
 130. Cephalixin
 131. Cephradine
35 132. Cefaclor
 133. Cefadroxil
 134. Cefatrizine

135. Cefroxadine

136. Cephaloglycin

c. Penicillin antibiotics like:

- 5 200. Benzylpenicillin
 201. Phenoxymethylpenicillin
 202. Phenethicillin
 203. Methicillin
 204. Nafcillin
10 205. Oxacillin
 206. Cloxacillin
 207. Dicloxacillin
 208. Flucloxacillin
 209. Azidocillin
15 210. Ampicillin
 211. Amoxycillin
 212. Epicillin
 213. Cyclacillin
 214. Carbenicillin
20 215. Ticarcillin
 216. Sulbenicillin
 217. Azlocillin
 218. Mezlocillin
 219. Piperazillin
25 220. Apalcillin
 221. Temocillin
 222. Carfecillin
 223. Carindacillin
 224. Hetacillin

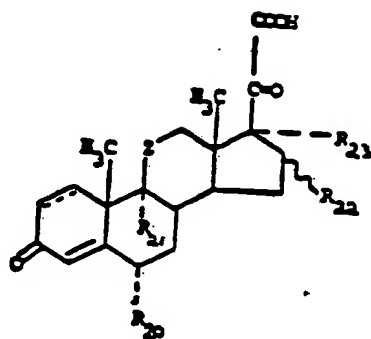
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d. 4-Quinolone antibiotics like:

300. Ciprofloxacin
 301. Norfloxacin
 302. Acrosoxacin
35 303. Pipemidic acid
 304. Nalidixic acid

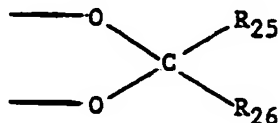
305. Enoxacin
 306. Ofloxacin
 307. Oxolinic acid
 308. Flumequine
 5 309. Cinoxacin
 310. Piromidic acid
 311. Pefloxacin

e. Steroidal monocarboxylic acids having the structural formula II:



II

wherein R_{20} is hydrogen, fluoro, chloro, or methyl; R_{21} is hydrogen, fluoro or chloro; R_{22} is hydrogen, methyl, hydroxy or $-\text{OCOR}_{24}$ wherein R_{24} is $\text{C}_1\text{-C}_7$ straight or branched alkyl or phenyl; R_{23} is hydrogen, hydroxy, or $-\text{OCOR}_{24}$ wherein R_{24} is as defined above, with the proviso that when R_{22} is hydroxy or $-\text{OCOR}_{24}$ and R_{23} is other than hydrogen, then R_{22} and R_{23} are identical; or R_{22} and R_{23} are combined to form a
 30 divalent radical of the type



III

wherein R_{25} and R_{26} , which can be the same or different, are each C_{1-7} straight or branched alkyl or phenyl; Z is carbonyl or β -hydroxymethylene; the wavy line at the 16-position indicates the α or β -configuration; and the dotted line in the ring A indicates that the 1,2-linkage is saturated or unsaturated.

A particularly preferred group of carboxylic acids of the formula II consists of the compounds wherein the structural variables represented by R_{20} , R_{21} , R_{22} , R_{23} and Z and the dotted and wavy lines are identical to those of a known anti-inflammatory steroid selected from the group consisting of hydrocortisone, betamethasone, dexamethasone, prednisolone, triamcinolone, fluocortolone, cortisone, fludrocortisone, chloroprednisone, flumethasone, fluprednisolone, meprednisone, methyl prednisolone, paramethasone, prednison, flurandrenolone acetone, amcinafal, amcinafide, clocortolone, desonide, desoximetasone, fluprednate, flunisolide, fluocinolone acetone, triamcinolone acetone, betamethasone 17-benzoate and betamethasone 17-valerate. Another preferred group of compounds of formula II consists of the compounds wherein the structural variables represented by R_{20} , R_{21} , R_{22} , Z and the dotted and wavy lines are identical to those of a known anti-inflammatory steroid selected from the group consisting of hydrocortisone, cortisone, fludrocortisone, betamethasone, chloroprednisone, dexamethasone, flumethasone, fluprednisolone, meprednisone, methyl prednisolone, paramethasone and prednisolone, and R_{23} is $-OCOR_{24}$ wherein R_{24} is as hereinbefore defined, most especially when R_{24} is CH_3 , C_2H_5 , C_3H_7 or phenyl. Yet another preferred group of parent acids of formula II consists of the compounds wherein the structural variables represented by R_{20} , R_{21} , Z and the wavy and dotted lines are identical to those of triamcinolone, and R_{22} and R_{23} are identical $-OCOR_{24}$ groupings wherein R_{24} is as hereinbefore defined, most especially when R_{24} is CH_3 , C_2H_5 , C_3H_7 or phenyl. Particularly preferred parent acids encompassed by formula II include

6 α -fluoro-11 β -hydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid;

9 α -fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3,20-dioxopregna-1,4-dien-21-oic acid;

9 α -fluoro-11 β ,17 α -dihydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid;

11 β ,17 α -dihydroxy-3,20-dioxopregn-4-en-21-oic acid;

9 α -fluoro-11 β ,16 α ,17 α -trihydroxy-3,20-dioxopregna-1,4-dien-21-oic acid; and

11 β ,17 α -dihydroxy-3,20-dioxopregna-1,4-dien-21-oic acid;

as well as the corresponding 17-esters of the specific 17-hydroxy compounds just named, most especially the 17-propionates, butyrates and benzoates thereof.

f. Prostaglandins like:

500. Prostaglandin E₂

501. Prostaglandin F_{2 α}

502. 15-Deoxy-16-hydroxy-16-vinylprostaglandin E₂

503. 11-Deoxy-11 α ,12 α -methanoprostaglandin E₂

504. 11-Deoxy-11 α ,12 α -difluoromethanoprostaglandin E₂

505. Prostacyclin

506. Epoprostenol

507. dl-16-Deoxy-16-hydroxy-16 (α/β)-vinyl prostaglandin E₂

508. Prostaglandin E₁

509. Thromboxane A₂

510. 16,16-Dimethylprostaglandin E₂

511. (15R)-15-Methylprostaglandin E₂ (Arbaprostil)

512. Meteneprost

513. Nileprost

514. Ciprostene

g. Angiotensin-converting enzyme inhibitors like:

600. (2R, 4R)-2-(2-Hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid

601. Enalaprilic acid (N-[1-(S)-carboxy-3-phenyl-propyl]-L-alanyl-L-proline)

602. Captopril

603. N-Cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-2-methyl-1-oxopropyl]glycine

604. 1-[4-Carboxy-2-methyl-2R,4R-pentanoyl]-2,3-dihydro-

2S-indole-2-carboxylic acid

605. Alecapril (1-[(S)-3-Acetylthio-2-methyl-propanoyl]-L-propyl-L-phenylalanine)
- 5 606. [3S-[2[R*(R*)]],3R*]-2-[2-[[1-carboxy-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid
607. [2S-[1[R*(R*)]],2 α ,3 α ,7 α]-1-[2-[[1-carboxy-3-phenylpropyl]-amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid.
- 10 608. (S)-Benzamido-4-oxo-6-phenylhexanoyl-2-carboxy-pyrrolidine
609. Lisinopril
610. Tiopronin
611. Pivopril

15 h. Various other bio-affecting carboxylic acid agents:

700. Ethacrynic acid
701. L-Tyrosine
702. α -Methyl-L-tyrosine
703. Penicillamine
- 20 704. Probenicid
705. 5-Aminosalicylic acid
706. 4-Aminobenzoic acid
707. Methyldopa
708. L-Dopa
- 25 709. Carbidopa
710. Valproic acid
711. 4-Aminobutyric acid
712. Moxalactam
713. Clavulanic acid
- 30 714. Tranexamic acid
715. Furosemide
716. 7-Theophylline acetic acid
717. Clofibric acid
718. Thienamycin
- 35 719. N-Formimidoylthienamycin
720. Amphotericin B
721. Nicotinic acid

722. Methotrexate
723. L-Thyroxine
724. Cromoglycic acid
725. Bumetanide
5 726. Folic acid
727. Chlorambucil
728. Melphalan
729. Fusidic acid
730. 4-Aminosalicylic acid
10 731. Liothyronine
732. Tretinoin
733. o-Thymotinic acid
734. 6-Aminocaproic acid
735. L-Cysteine
15 736. Tranilast (N-(3',4'-dimethoxycinnamoyl)anthranilic acid)
737. Baclofen
738. 4-Amino-5-ethyl-3-thiophenecarboxylic acid
739. N-Cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-2-methyl-1-oxopropyl]glycine
20 740. Isoguvacine
741. Nipecotic acid
742. D-Eritadenine [(2R,3R)-4-adenin-9-yl-2,3-dihydroxybutanoic acid]
743. (RS)-3-Adenin-9-yl-2-hydroxypropanoic acid
25 744. 1-[4-Carboxy-2-methyl-2R,4R-pentanoyl]-2,3-dihydro-2S-indole-2-carboxylic acid
745. Phenylalanylalanine
746. Glafenic acid
747. Floctafenic acid
30 748. N-(Phosphonoacetyl)-L-aspartic acid (PALA)
749. Proxicromil
750. Cysteamine
751. N-Acetylcysteine
752. Proglumide
35 753. Aztreonam
754. Mecillinam
755. All-trans-retinoic acid

756. 13-cis-retinoic acid
757. Isonipecotic acid
758. Anthracene-9-carboxylic acid
759. α -Fluoromethylhistidine
5 760. 6-Amino-2-mercapto-5-methylpyrimidine-4-carboxylic acid
761. Glutathione
762. Acivicin
763. L- α -Glutamyl dopamine
764. 6-Aminonicotinic acid
10 765. Loflazepate
766. 6-[[1(S)-[3(S),4-dihydro-8-hydroxy-1-oxo-1H-2-benzopyran-3-yl]-3-methylbutyl]amino]-4-(S),5(S)-dihydroxy-6-oxo-3(S)-ammoniohexanoate
767. 2-2-Isovaleramidobut-2-enoic acid
15 768. D,L-2,4-Dihydroxyphenylalanine
769. L-2-Oxothiazolidine-4-carboxylic acid
770. Iopanoic acid
771. 4-Aminomethylbenzoic acid
772. 4-Hydroxybenzoic acid
20 773. 4-Hydroxybutyric acid
774. Ticrynafen
775. 4-amino-3-phenylbutyric acid
776. 4-(Dimethylamino)benzoic acid
777. Capobenic acid
25 778. Pantothenic acid
779. Folinic acid
780. Orotic acid
781. Biotin
782. Mycophenolic acid
30 783. Thiocitic acid
784. Pyroglutamic acid
785. Oleic acid
786. Linoleic acid
787. Cholic acid
35 788. Naturally occurring amino acids (e.g. glycine, histidine, phenylalanine and glutamic acid)
789. N,N-Dimethylglycine

790. Salazosulfapyridine

791. Azodisal

792. Isotretinoin

793. Etretinic acid

5

All of the above compounds are known in the art in the acid or salt form.

10

While all of the compounds encompassed by formula I essentially satisfy the objectives of the present invention, preferred compounds include those derived from the following compounds (compounds A)

1. Acetylsalicylic acid

2. Salicylic acid

3. Sulindac

15

4. Indomethacin

5. Naproxen

7. Ibuprofen

8. Ketoprofen

11. Diflunisal

20

12. Tolmetin

13. Flurbiprofen

15. Mefenamic acid

21. Suprofen

31. Tolfenamic acid

25

119. Cefmetazole

104. Cefazolin

130. Cephalexin

132. Cefaclor

30

133. Cefuroxime

134. Cefamandole

118. Cefoxitin

200. Benzylpenicillin

201. Phenoxymethylpenicillin

35

210. Ampicillin

211. Amoxycillin

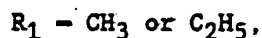
214. Carbenicillin

217. Azlocillin
219. Piperacillin
- 5 6 α -Fluoro-11 β -hydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
9 α -Fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
9 α -Fluoro-11 β ,17 α -dihydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
10 11 β ,17 α -Dihydroxy-3,20-dioxopregn-4-en-21-oic acid
9 α -Fluoro-11 β ,16 α ,17 α -trihydroxy-3,20-dioxopregna-4-dien-21-oic acid
11 β ,17 α -Dihydroxy-3,20-dioxopregna-1,4-dien-21-oic acid.
- 15 500. Prostaglandin E₂
501. Prostaglandin F_{2 α}
508. Prostaglandin E₁
505. Prostacyclin
511. (15R)-15-Methylprostaglandin E₂ (Arbaprostil)
513. Nileprost
20 514. Ciprostone
601. Enalaprilic acid
602. Captopril
603. N-Cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-2-methyl-1-oxopropyl]glycine
25 604. 1-[4-Carboxy-2-methyl-2R,4R-pentanoyl]-2,3-dihydro-2S-indole-2-carboxylic acid
607. [2S-[1[R*(R*)]],2 α ,3 α ,7 α]-1-[2-[[1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]octahydro-1H-indole-2-carboxylic acid
30
705. 5-Aminosalicylic acid
707. Methyl dopa
708. L-Dopa
710. Valproic acid
35 714. Tranexamic acid
715. Furosemide

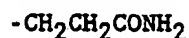
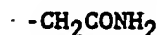
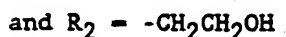
722. Methotrexate
 727. Chlorambucil
 717. Clofibrilic acid
 720. Amphotericin B
 5 734. 6-Aminocaproic acid
 754. Mecillinam
 732. Tretinoin
 771. 4-Aminomethylbenzoic acid
 782. Mycophenolic acid
 10 768. D,L-2,4-Dihydroxyphenylalanine

Particularly preferred compounds of the invention include those wherein R-COO is derived from one of the specific bio-affecting acids named above, n is 1 and R₁ and R₂ are as defined in connection with the general formula I.
 15

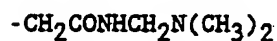
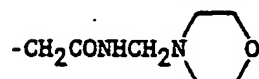
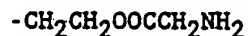
In especially preferred compounds of the formula I, R-COO is derived from one of the compounds A above, n = 1, and



20



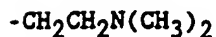
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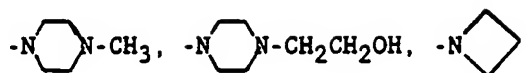
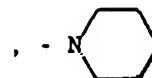
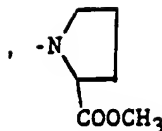
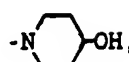
30



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or $-\text{NR}_1\text{R}_2$ is



It will be appreciated that in the especially preferred compounds defined immediately above, each and every possible combination between the given examples of R_1 and R_2 in the derivative group $-\text{CH}_2\text{CONR}_1\text{R}_2$ may, of course, be combined with each and every group $\text{R}-\text{COO}$ derived from the compounds A listed above, and that the above definition is equivalent to listing each and every possible combination of the listed examples of $\text{R}-\text{COO}$, R_1 and R_2 .

The invention further concerns compounds of the general formula I as defined above wherein R_1 and R_2 both are alkyl or both are $-\text{CH}_2\text{CH}_2\text{OH}$, and

$\text{R}-\text{COO}-$ is the acyloxy residue of one of the following bio-affecting carboxylic acid agents (compounds B)

2. Salicylic acid

3. Sulindac

4. Indomethacin

5. Naproxen

7. Ibuprofen

8. Ketoprofen

11. Diflunisal

12. Tolmetin

13. Flurbiprofen

15. Mefenamic acid
21. Suprofen
31. Tolfenamic acid
- 5 119. Cefmetazole
104. Cefazolin
130. Cephalexin
132. Cefaclor
133. Cefuroxime
134. Cefamandole
10 118. Cefoxitin
200. Benzylpenicillin
201. Phenoxymethylpenicillin
210. Ampicillin
15 211. Amoxycillin
214. Carbenicillin
217. Azlocillin
219. Piperacillin
- 20 6 α -Fluoro-11 β -hydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
9 α -Fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
9 α -Fluoro-11 β ,17 α -dihydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
25 11 β ,17 α -Dihydroxy-3,20-dioxopregn-4-en-21-oic acid
9 α -Fluoro-11 β ,16 α ,17 α -trihydroxy-3,20-dioxopregna-4-dien-21-oic acid
11 β ,17 α -Dihydroxy-3,20-dioxopregna-1,4-dien-21-oic acid.
- 30 500. Prostaglandin E₂
501. Prostaglandin F_{2 α}
508. Prostaglandin E₁
505. Prostacyclin
- 35 511. (15R)-15-Methylprostaglandin E₂ (Arbaprostil)
513. Nileprost
514. Ciprostone

601. Enalaprilic acid
602. Captopril
603. N-Cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-
-2-methyl-1-oxopropyl]glycine
5 604. 1-[4-Carboxy-2-methyl-2R,4R-pentanoyl]-2,3-dihydro-
-2S-indole-2-carboxylic acid
607. [2S-[1[R*(R*)]],2 α ,3 α ,7 α]-1-[2-[[1-carboxy-3-phenyl-
propyl]amino]-1-oxopropyl]octahydro-1H-indole-2-
carboxylic acid
10 705. 5-Aminosalicylic acid
707. Methyldopa
708. L-Dopa
710. Valproic acid
15 714. Tranexamic acid
715. Furosemide
722. Methotrexate
727. Chlorambucil
717. Clofibric acid
20 720. Amphotericin B
734. 6-Aminocaproic acid
754. Mecillinam
732. Tretinoin
771. 4-Aminomethylbenzoic acid
25 782. Mycophenolic acid
768. D,L-2,4-Dihydroxyphenylalanine

When R₁ and R₂ are both alkyl, they may be the same or different and
are preferably C₁₋₃ alkyl such as methyl, ethyl, n-propyl or iso-
30 propyl. It is further preferred that n = 1. It will be appreciated
that in such preferred compounds, each and every possible combination
of R₁ and R₂ (i.e. both being -CH₂CH₂OH, or R₁ and R₂ individually
being selected from methyl, ethyl, propyl and isopropyl) in the
derivative group -CH₂CONR₁R₂ may, of course, be combined with each
35 and every group R-COO derived from the compounds B listed above, and
that the above definition is equivalent to listing each and every

possible combination of the listed examples of R-COO (from compounds B), R₁ and R₂.

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DETAILED DESCRIPTION OF THE INVENTION

Dosage forms and dose

5 The prodrug compounds of formula I of the present invention can be used to treat any condition for which the parent carboxylic group containing drug, medicament or pharmaceutical is useful. For example, if naproxen is the parent drug of choice, the ester prodrug can be used for any condition or treatment for which naproxen would be
10 administered.

Thus, the prodrug compounds of formula I may be administered orally, topically, parenterally, rectally or by inhalation spray in dosage forms or formulations containing conventional, non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The formulation and preparation of any of this broad spectrum of dosage
15 forms into which the subject prodrugs can be disposed is well-known to those skilled in the art of pharmaceutical formulation. Specific information can, however, be found in the text entitled "Remington's Pharmaceutical Sciences", Sixteenth Edition, 1980.
20

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.
25 Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide a
30 pharmaceutically elegant and palatable preparation.

Formulations for oral use include tablets which contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents,
35 such as calcium carbonate, sodium chloride, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents,

- for example, potato starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.
- Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.
- Aqueous suspensions usually contain the active materials in admixture with appropriate excipients. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally-occurring phosphatide, for example, lecithin; a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecan-2-yl ethyleneoxycetanol; a condensation product of ethylene oxide with a partial ester derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate; or a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, methyl, ethyl or n-propyl p-hydroxybenzoate; one or more colouring agents; one or more flavouring agents; and one or more sweetening agents such as sucrose or saccharin.
- Oily suspension may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily

suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oils, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gum tragacanth; naturally-occurring phosphatides, for example, soybean lecithin; and esters including partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic

sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids such as oleic acid also find use in the preparation of injectibles.

The compounds of formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug, for example, cocoa butter, or *adepts solidus* polyethylene glycols.

For topical use, creams, ointments, jellies, solutions, suspensions or the like containing the prodrugs are employed according to methods recognized in the art.

Naturally, therapeutic dosage range for the compounds of the present invention will vary with the size and needs of the patient and the particular pain or disease symptom being treated. However, generally speaking, the following dosage guidelines will suffice. On an oral basis, the therapeutic dose required for a compound of the present invention will generally, on a molecular basis, mimic that for the parent carboxylic acid drug. On a topical basis, application of an 0.01% to 5% concentration of a compound of the present invention (in a suitable topical carrier material) to the affected site should suffice.

From the foregoing description, one of ordinary skill in the art can easily ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes and/or modifications of the invention to adapt it to various usages and conditions. As such, these changes and/or modifications are properly, equitably and intended to be within the full range of equivalence of the following claims.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon

the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 5 mg to 5 gm of the active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total composition. Other dosage forms such as ophthalmic dosage forms contain less active ingredient such as for example from 0.1 mg to 5 mg. Dosage unit forms will generally contain between from about 0.1 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and severity of the particular disease undergoing therapy.

Preparation of the prodrugs of formula I

The compounds of the present invention can be prepared by a variety of synthetic routes. A generally applicable process (method a) comprises reacting the carboxylic acid agent of the formula A or a salt (e.g. a metal salt) thereof



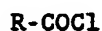
wherein $R - COO -$ is defined as above in connection with formula I, with a compound having the formula B:



wherein n , R_1 and R_2 are as defined above and X is a suitable leaving group (e.g., halogen such as Cl, I or Br, or a methanesulfonyloxy or toluenesulfonyloxy group). The reaction is preferably carried out in a solvent (e.g. N,N-dimethylformamide, water, acetonitrile, a lower

alcohol, ethyl acetate, toluene or the like). An equivalent of an organic base such as triethylamine, tetramethylguanidine or the like is typically added or crown ethers are used as phase-transfer catalysts. If X in formula B is chlorine catalytic amounts of an iodide salt may be added to the reaction mixture. The reaction is carried out at a temperature of from room temperature to the boiling point of the solvent, and for a period of time of 0.5 to 48 hours.

Another method (method b) for preparing compounds of the invention comprises reacting a compound of the formula B, wherein X is hydroxy, with an acid of the formula A or with the corresponding acid chloride of the formula C



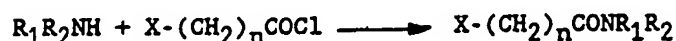
(C)

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When an acid starting material is used, i.e. a compound of formula A, the reaction is conducted in the presence of a suitable dehydrating agent, for example N,N-dicyclohexylcarbodiimide. The reaction utilizing an acid starting material is conveniently carried out in an inert solvent such as dichloromethane, dioxane, pyridine or the like, at a temperature of from 0° to 60°C, for from 1 to 48 h. A catalyst such as p-toluenesulphonic acid or 4-(N,N-dimethylamino)pyridine may be added. When the reaction utilizes an acid chloride starting material, the process can be conveniently carried out by reacting the compound of formula B, wherein X is hydroxy, with the desired acid chloride in an inert solvent such as benzene, dichloromethane, dimethylformamide, acetone, dioxane, acetonitrile or the like, at from room temperature to reflux, for from 1 to 24 h, in the presence of an acid scavenger such as an alkali metal carbonate, or an organic base such as triethylamine or pyridine.

The acid chlorides of formula C which can be used in the above method are prepared from the corresponding acids by known means, e.g. by treatment of the acid with thionyl chloride or oxalyl chloride. Instead of acid chlorides acid anhydrides or mixed anhydrides may be used.

The starting materials of formula B, in which X is a halogen, are also prepared by known means, e.g. by treatment of the appropriate amine with an appropriately halogen-substituted acid chloride, acid anhydride or ester as represented by the following chemical equation
5 for an acid chloride:



10

Several compounds of formula B, in which X is a halogen, and methods for their preparation, have been described in the literature, see e.g. Hankins (1965), Weaver and Whaley (1947), Ronwin (1953), Berkelhammer et al. (1961) and Speziale and Hamm (1956).

15

The starting materials of formula B, in which X is hydroxy, are also prepared by known means, e.g. by hydrolysis of 2-(acetoxymethyl)acetamides or 2-(benzoyloxymethyl)acetamides. Specific examples are given below.

20

Several compounds of formula B, in which X is hydroxy, and methods for their preparation, have been described in the literature, see e.g. DE Offen. 2,904,490, DE 2,201,432, and DE 2,219,923.

A third method (method c) for preparing compounds of the present invention comprises reacting a compound of the formula D
25



(D)

30

wherein R_1 and R_2 are as defined above in connection with formula I, with an acid of the formula E

35



wherein R-COO- and n are as defined above in connection with formula
5 I, or with the corresponding acid chloride (or acid anhydrides) of
the formula F



10 When a compound of formula E is used, the reaction is conducted in
the presence of a suitable dehydrating agent, e.g. N,N-dicyclohexyl-
carbodiimide. The reaction is conveniently carried out in an inert
solvent such as dichloromethane, dioxane, pyridine or the like, at a
15 temperature of from 0° to 60°C, for from 1 to 48 h. When the reaction
utilizes an acid chloride starting material of formula F, the process
can be conveniently carried out by reacting the compound of formula F
with the desired amine or amine salt in a solvent such as benzene,
dichloromethane, dimethylformamide, acetone, dioxane, acetonitrile,
20 water or the like, at from 0°C to reflux, for from 1/2 to 24 h, in
the presence of an acid scavenger such as alkali metal carbonate, or
an organic base such as triethylamine, or an excess of the amine.

The acid chlorides of formula F which can be used in the above method
are prepared from the corresponding acids by known means, e.g. by
25 treatment of the acid with thionyl chloride or oxalyl chloride.

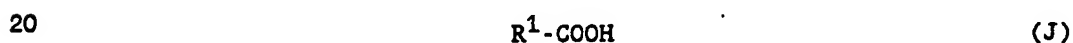
The acids of formula E which can be used in the above method are
prepared from the parent acids (i.e. R - COOH) by known means, e.g.
by reacting the acid or a salt of the acid (e.g. a metal or
30 trimethylammonium salt) with compounds of the formula G



35 wherein X and n are as defined above, or with compounds of the for-
mula H



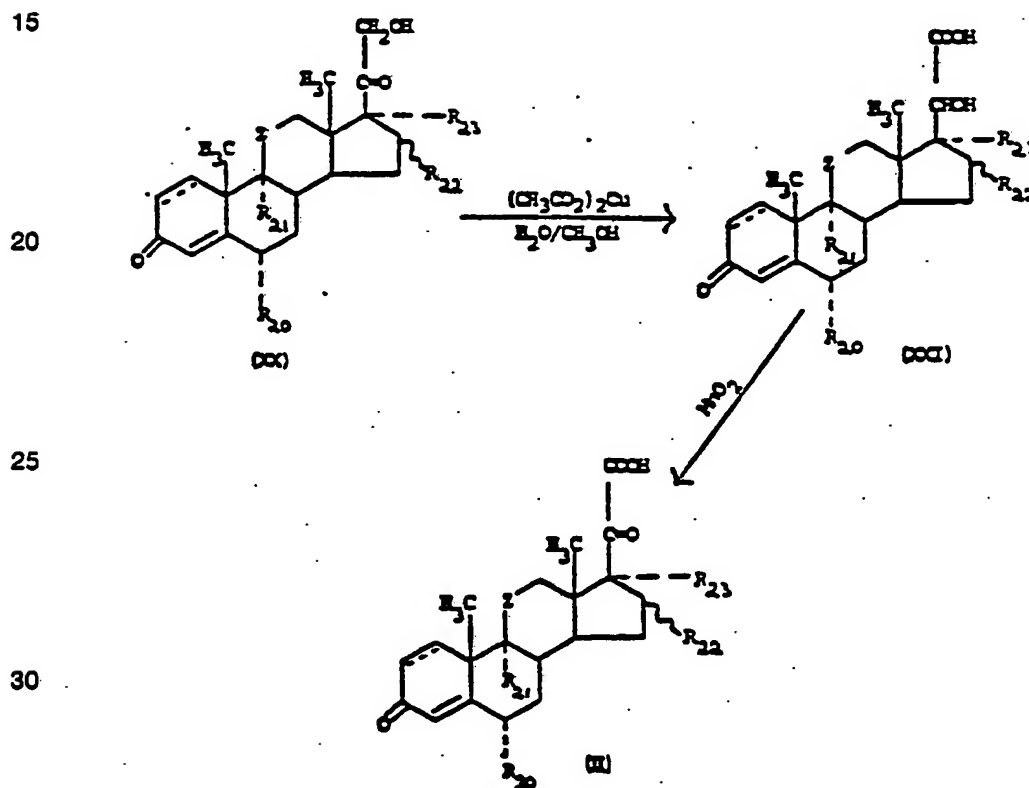
- 5 wherein X and n are as defined above. The intermediates obtained therefrom, i.e. $R-COO-(CH_2)_nCOOCH_2C_6H_5$ and $R-COO-(CH_2)_n-CONH_2$, are subsequently transformed to the compounds of formula E by e.g. hydrogenation or acidic hydrolysis. Several compounds of formula E and methods for preparing them are known from the literature, see e.g. Boltze et al. (1980) and Concilio & Bongini (1966).
- 10 While the basic methods described above can be used to prepare any of the compounds of the invention, certain conditions and/or modifications therein are made in specific instances. Thus, for example, the basic methods may be modified in the cases where the desired product of formula I contains free aliphatic amino, thiol or hydroxyl group-
- 15 ings which, if present in the acid starting material, would undergo undesired side reaction and/or would interfere with the desired course of the above-described ester formation. In such cases, the compounds of formula B or D are reacted with an acid of the formula J



- 20 wherein R^1-COO- is the amino-, thiol- or hydroxyl-protected acyloxy residue of a carboxylic acid agent ($R-COOH$) containing amino, thiol or hydroxyl groups. The amino, hydroxy or thiol function in the
- 25 parent acids of the formula $RCOOH$ are converted to their protected counterparts in formula J by known methods, e.g. those known in the art of peptide synthesis. For example, amino groups are conveniently protected by the carbobenzoxy carbonyl or t-butyloxycarbonyl group.
- 30 The compound of formula J, its corresponding acid chloride or protected counterpart for formula E is subsequently reacted with a compound of formula B or D, as described supra, to afford the compound corresponding to formula I, but containing a protected acyloxy residue, i.e. R^1-COO- as defined above in place of $R-COO-$ in formula
- 35 I. That protected compound is then deprotected by known methods, e.g. by hydrogenation or hydrolysis.

The above-described process variations involving the addition and ultimate removal of protecting groups is only used when the free amino, hydroxy and/or thiol functions are in need of protection.

- 5 When the starting acid of formula I hereinabove is a steroidal acid of formula II, this can be prepared by methods known in the art, for example by the methods described in US Patent No. 4,164,504 (Varma). See also Chemical Abstracts, 83, 179407 and 84, 122146. Thus, the following reaction scheme is illustrative of a general method for
- 10 preparing the desired acids:



wherein R_{20} , R_{21} , R_{22} , R_{23} , Z and the dotted and wavy lines are defined as before. In the cupric acetate reaction, water is used as a co-solvent with a suitable alcohol, e.g. methanol or other lower alkanol, and the reaction is allowed to proceed for an extended period of time (more than 24 hours), since decreasing the water present and lessening reaction time tend to favour formation of the 21-ester of the steroid with the alcohol employed. Also, oxygen or air is bubbled through the mixture during the course of the reaction to encourage formation of 21-acid rather than 21-aldehyde. In the second step, the 20-hydroxy group is oxidized to a 20-keto function by reacting the steroid of formula XXI with manganese dioxide or lead dioxide in an inert halogenated hydrocarbon solvent such as chloroform or dichloromethane.

DESCRIPTION OF THE DRAWINGS

Fig. 1 shows time courses for naproxen N,N-dimethylglycolamide ester (*) and naproxen (o) during hydrolysis of the ester in 80% human plasma at 37°C. The initial ester concentration was 10^{-4} M.

Fig. 2 shows plots of the first-order kinetics of hydrolysis of various esters (initial concentration being 10^{-4} M) in 80% human plasma at 37°C. Key: o, N,N-diethylglycolamide ester of L-phenylalanine;

*, N,N-diethylglycolamide ester of naproxen; Δ , N-methyl, N-carbamoylmethylglycolamide ester of ketoprofen.

Fig. 3 shows plot of the rate of hydrolysis of the N,N-dimethylglycolamide ester of salicylic acid in 80% human plasma at 37°C.

The present invention is further illustrated by the following examples which, however, are not construed to be limiting. The derivatives described all had spectroscopic properties (IR and ^1H NMR) and elemental analysis (C, H and N) in agreement with their structures.

EXAMPLE 1

2-(Benzoyloxy)-N,N-dimethylacetamide

Benzoic acid (2.44 g, 0.02 mole) and 2-chloro-N,N-dimethylacetamide (2.43 g, 0.02 mole) were dissolved in 10 ml of N,N-dimethylformamide. Sodium iodide (150, 2 mmol) and triethylamine (2.02 g, 0.02 mole) were added and the mixture was stirred at room temperature (20-25°C) overnight. After addition of 50 ml of water the reaction mixture was extracted twice with ethyl acetate. The combined extracts were washed with a diluted solution of sodium thiosulphate, a 2% aqueous solution of sodium bicarbonate, water, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was recrystallized from ethanol-water to give 3.5 g (85%) of the title compound. Mp 81-82°C.

EXAMPLE 2

The compound in Example 1 was also prepared by the following procedure:

2-Chloro-N,N-dimethylacetamide (12.16 g, 0.1 mole) was added to a solution of sodium benzoate (14.4 g, 0.1 mole) and sodium iodide (3.75 g, 0.025 mole) in 75 ml of water. The reaction solution was refluxed for 2 h. Upon standing overnight at 4°C the title compound precipitated. It was filtered off, washed with water and recrystallized from aqueous ethanol (15.7 g; 76%). Mp 81-82°C.

EXAMPLE 3

(Benzoyloxy)acetyl chloride

2-Chloroacetamide (18.7 g, 0.2 mole) was added to a solution of sodium benzoate (28.8 g, 0.2 mole) and sodium iodide (7.5 g, 0.05 mole) in 150 ml of water. The mixture was stirred at 90°C for 14 h.

Upon cooling to 4°C 2-(benzoyloxy)acetamide precipitated and was isolated by filtration. Recrystallization from ethanol-water yielded 32.2 g (90%). Mp 120.5-121°C.

5 2-(Benzoyloxy)acetamide (19.7 g, 0.11 mole) was added to 200 ml of 7.8 M hydrochloric acid. The mixture was stirred at 75°C for 10 min. Upon cooling 2-(benzoyloxy)acetic acid precipitated. It was isolated by filtration, dried and recrystallized from benzene (15.8 g, 80%), Mp 111-112°C.

10 A mixture of 2-(benzoyloxy)acetic acid (12.6 g) and thionyl chloride (15 ml) was refluxed for 3 h. Excess of thionyl chloride was removed in vacuo and the crude (benzoyloxy)acetyl chloride obtained was purified by distillation in vacuo. The yield was 88%. Mp 25-26°C.

15 **EXAMPLE 4**

2-(Benzoyloxy)-(N-methyl-N-ethoxycarbonylmethyl)acetamide

A solution of (benzoyloxy)acetyl chloride (0.8 g, 4 mmole) in 4 ml of benzene was added to a cooled (about 5°C) solution of sarcosine ethyl ester hydrochloride (0.84 g, 12 mmole) in 6 ml of 2 M sodium hydroxide. The mixture was stirred vigorously at room temperature for 2 h. The layers were separated and the aqueous phase re-extracted with ethyl acetate (20 ml). The combined organic extracts were washed with 2 M hydrochloric acid (10 ml), and dried. Evaporation in vacuo afforded an oily residue which crystallized by trituration with petroleum ether at -20°C.

20

25

Recrystallization from ether-petroleum ether yielded the title compound (0.68 g, 61%). Mp 39-40°C.

30

EXAMPLE 5

1-Methyl-4-(benzoyloxyacetyl)piperazine hydrochloride

A solution of 1-methylpiperazine (0.40 g, 4 mmole) in 5 ml benzene was added dropwise while stirring to a solution of (benzoyloxy)acetylchloride (0.80 g, 4 mmole) in 10 ml of benzene. After the addition was completed (about 10 min) the reaction mixture was stirred

35

at room temperature for 1 h. Ether (10 ml) was added and the mixture was filtered. The white crystalline compound on the filter was washed with ether and finally recrystallized from ethanol, yielding 0.70 g (59%) of the title compound. Mp 227-228°C.

5

EXAMPLE 6

2-(Benzoyloxy)-(N-methyl-N-β-hydroxyethyl)acetamide

A solution of (benzoyloxy)acetyl chloride (1.5 g, 8 mmole) in 8 ml of benzene was mixed with N-methylethanolamine (1.8 g, 24 mmole). The solution was stirred at room temperature for 3 h and then concentrated in vacuo. The residue was dissolved in ethyl acetate (50 ml) and water (10 ml). The layers were separated and the organic phase washed with 2 M hydrochloric acid (5 ml), water (5 ml), dried and evaporated in vacuo. The residue crystallized by trituration with ether and standing overnight at -20°C. The compound was filtered off and recrystallized from ethyl acetate-petroleum ether, giving 1.1 g (50%) of the title compound. Mp 78-80°C.

20

EXAMPLE 7

2-(Benzoyloxy)-N,N-(dicarbamoylmethyl)acetamide

A solution of (benzoyloxy)acetyl chloride (0.8 g, 4 mmole) in benzene (4 ml) was added while stirring at room temperature to a mixture of iminodiacetamide hydrochloride (1.06 g, 6 mmole) and sodium bicarbonate (2.52 g, 30 mmole) in water (5 ml). The mixture was stirred for 3 h. The precipitate formed was filtered off, washed with a small amount of water and recrystallized from water to give 0.70 g (60%) of the title compound. Mp 195-196°C.

30

EXAMPLE 8

N-(Benzoyloxymethylcarbonyl)pyrrolidone

A mixture of (benzoyloxy)acetyl chloride (1.98 g, 0.01 mole), pyrrolidone (0.85 g, 0.01 mole) and pyridine (0.8 g, 0.01 mole) in acetone (10 ml) was refluxed for 3 h. The cooled mixture was filtered and evaporated in vacuo. The residue was dissolved in ethyl acetate

35

- (50 ml) and the solution washed with a 2% aqueous solution of sodium bicarbonate, 2 M hydrochloric acid and water. After drying over anhydrous sulphate, the organic phase was evaporated under reduced pressure to give a residue which crystallized by addition of ether.
- 5 Recrystallization from ether-petroleum ether yielded 1.6 g (65%) of the title compound. Mp 83-84°C.

EXAMPLES 9-33

- 10 By following the procedures of the foregoing examples several more esters of benzoic acid according to the invention were prepared. The structure of these esters and their melting points are shown in Table 1.

15 EXAMPLE 34

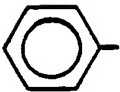
2-[1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyloxy]-
N,N-diethylacetamide

- Indomethacin (1.43 g, 4 mmole) and 2-chloro-N,N-diethylacetamide
- 20 (0.61 g, 4.1 mmole) were dissolved in 5 ml of N,N-dimethylformamide and triethylamine (0.56 ml, 4 mmole) and sodium iodide (60 mg) added. The mixture was stirred at room temperature for 20 h and poured into 50 ml of water. The mixture was extracted with ethyl acetate (2 x 50 ml). The extract was washed with 2% aqueous solution bicarbonate
- 25 and water. After drying over anhydrous sodium sulphate the organic phase was evaporated in vacuo. The residue was recrystallized from ethyl acetate-petroleum ether, yielding 1.6 g (90%) of the title compound. Mp 148-149°C.

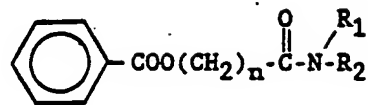
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35

TABLE 1

Compounds of Formula I wherein R -  , i.e.

5

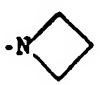
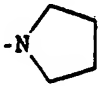
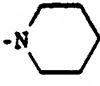
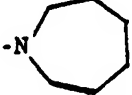

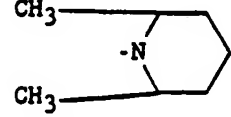
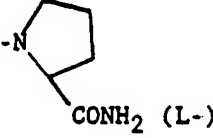
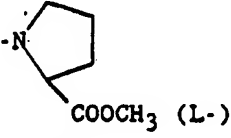
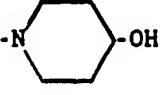
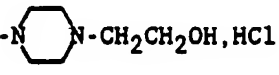
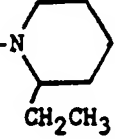


	Example number	n	R ₁	R ₂	Mp(°C)
10					
15	9	1	CH ₃	C ₂ H ₅	-20
	10	1	C ₂ H ₅	C ₂ H ₅	62.5-63.5
	11	1	C ₃ H ₇	C ₃ H ₇	-20
	12	1	iC ₃ H ₇	iC ₃ H ₇	104.5-105.5
	13	1	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂	42-43
	14	1	nC ₄ H ₉	nC ₄ H ₉	-25
	15	1	iC ₄ H ₉	iC ₄ H ₉	44-45
	16	1	CH ₃	CH ₂ CH ₂ OH	78-80
20	17	1	CH ₂ CH ₂ OH	CH ₂ CH ₂ OH	80-82
	18	1	CH ₃	CH ₂ CONH ₂	101-102
	19	1	CH ₃	C ₆ H ₁₁	100-101
	20	1	C ₆ H ₁₁	C ₆ H ₁₁	162-163
	21	2	CH ₃	CH ₃	<20
25	22	3	CH ₃	CH ₃	40-41
	23	1	C ₂ H ₅	CH ₂ CH ₂ OH	79-80
	23a	1	CH ₃	CH ₂ CH ₂ N- -(CH ₃) ₂ , HCl	158-159
	23b	1	CH ₂ CH ₂ OCH ₃	CH ₂ CH ₂ OCH ₃	57-58

30

35

TABLE 1 (continued)

	Example number	n	R ₁	Mp(°C)
5	24	1		74-75
10	25	1		57.5-58
	26	1		87-88
15	27	1		107-108
	28	1		103-104
20	29	1		118-118.5
	30	1		194-195
25	31	1		72-73
	32	1		121-122
30	33	1		228-229
	33a	1		54-55
35				

EXAMPLE 35

2-[(+)-6-Methoxy- α -methyl-2-naphthaleneacetyloxy]-
N,N-diethylacetamide

- 5 Naproxen (1.07 g, 5 mmole) and 2-chloro-N,N-diethyl-acetamide
(0.90 g, 6 mmole) were dissolved in 7 ml of N,N-dimethylformamide and
triethylamine (1.4 ml, 10 mmole) and sodium iodide (76 mg) were
added. The mixture was refluxed for 2 h, cooled and poured into 35 ml
10 of water. The precipitate formed after standing overnight at 4°C was
collected by filtration, washed with water and recrystallized from 95%
ethanol, yielding 1.5 g (92%) of the title compound. Mp 89-89.5°C.

EXAMPLE 36

2-[2-(Acetyloxy)benzoyloxy]-N,N-diethylacetamide

- 15 To a mixture of acetylsalicylic acid (5.4 g, 0.03 mole) and 2-chloro-
N,N-diethylacetamide (4.5 g, 0.03 mole) in 40 ml of ethyl acetate was
added triethylamine (4.2 ml, 0.03 mole) and sodium iodide (0.45 g,
0.003 mole). The mixture was refluxed for 4 h. After cooling the
20 mixture was filtered and the filtrate washed with 2 M hydrochloric
acid, 5% sodium bicarbonate and water. After drying over anhydrous
sodium sulphate the solution was evaporated in vacuo leaving an oil
which crystallized by trituration with ethanol. Recrystallization
from 80% ethanol afforded 6.2 g (70%) of the title compound. Mp 75-
25 76°C.

EXAMPLE 37

2-[2-Hydroxybenzoyloxy]-(N-methyl-N-carbamoylmethyl)-acetamide

- 30 The ester was prepared from salicylic acid and N-chloroacetyl-
sarcosinamide (prepared as described in Example 87) by the procedure
described in Example 1. The crude product was recrystallized from
ethyl acetate-ether. Mp 142-143°C.

EXAMPLE 38

2-(L-Phenylalanyloxy)-N,N-diethylacetamide hydrobromide

A solution of N-benzyloxycarbonyl-L-phenylalanine (3.0 g, 0.01 mole),
2-chloro-N,N-diethylacetamide (1.57 g, 0.011 mole) and triethylamine
5 (1.4 ml, 0.01 mole) in acetonitrile (15 ml) was refluxed for 6 h,
evaporated to dryness in vacuo, and diluted with saturated aqueous
sodium bicarbonate solution. N-Benzyloxycarbonyl-L-phenylalanine N,N-
diethylglycolamide ester was collected by filtration, washed with
10 water and recrystallized from ethanol-water. Mp 85.5-86.5°C.

This compound (2.0 g) was treated with 10 ml of 33% hydrogen bromide
in acetic acid for 1 h at room temperature. Addition of ether pre-
cipitated the title compound, which was washed with ether and recry-
stallized from methanol-ether. Mp 95-97°C.

15

EXAMPLE 39

2-[1-(p-Chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyloxy]-N,N-dimethylacetamide

20 a. To a stirred suspension of indomethacin (3.58 g, 0.01 mole) in
benzene (10 ml) at 60°C was added dropwise thionyl chloride
(1.12 ml, 0.015 mole). The mixture was stirred for 1 h at 65-70°C
and concentrated to about 5 ml in vacuo. Hot petroleum ether
(25 ml) was added and the mixture filtered to give 3.2 g (85%) of
25 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetyl chloride
(acid chloride of indomethacin). Mp 126-127°C.

b. 2-Hydroxy-N,N-dimethylacetamide was prepared by alkaline hydro-
lysis of 2-(benzoyloxy)-N,N-dimethylacetamide obtained as
30 described in Example 1. 2-(Benzoyloxy)-N,N-dimethylacetamide
(20.7 g, 0.1 mole) was dissolved in 50 ml of ethanol by heating to
40-50°C. Potassium hydroxide (2 M, 70 ml) was added and the mix-
ture allowed to stand at room temperature for 1 h. The pH of the
solution was adjusted to 8-9 by addition of 4 M hydrochloric acid
35 and the ethanol removed in vacuo. The pH of the mixture was ad-
justed to 3.5-4 with hydrochloric acid. Precipitated benzoic acid
was filtered off and the filtrate was made alkaline (pH 8-9) with

potassium hydroxide. The solution was evaporated in vacuo. The semi-solid residue obtained was slurried in ethyl acetate (100 ml) and the mixture heated to about 60°C. It was filtered, dried over sodium sulphate and evaporated in vacuo to give crude 2-hydroxy-N,N-dimethylacetamide. This extraction process was repeated twice. Recrystallization from ether-petroleum ether afforded 7.1 g (69%) of the compound. Mp 49-50°C.

c. Indomethacin acid chloride (1.14 g, 3 mmole) was added in portions to a solution of 2-hydroxy-N,N-dimethylacetamide (340 mg, 3.3 mmole) in acetonitrile (3 ml) and pyridine (320 g, 4 mmole), cooled to 0-4°C. The mixture was stirred at room temperature for 4 h and evaporated in vacuo. The residue was taken up in a mixture of water and ethyl acetate. The organic base was separated and washed with 1 M hydrochloric acid, 5% sodium bicarbonate and water. Evaporation of the dried solution afforded a solid residue which upon recrystallization from ethyl acetate afforded the title compound. Mp 149-150°C.

20 EXAMPLE 40

2-(4-Aminobenzoyloxy)-N,N-diethylacetamide

A mixture of 4-aminobenzoic acid (1.37 g, 0.01 mole), 2-chloro-N,N-diethylacetamide 2.0 ml, 0.015 mole) and 1.8-diazabicyclo[5.4.0]-undec-7-ene (1.52 g, 0.01 mole) in benzene (20 ml) was stirred at 80°C for 4 h and then evaporated in vacuo. The residue was taken up in ethyl acetate. After washing with 5% sodium bicarbonate and water the ethyl acetate extract was dried and evaporated in vacuo leaving crude title compound. Recrystallization from ethanol-water gave 1.5 g (60%). Mp 135-136°C.

EXAMPLE 41

2-[α -Methyl-4-(2-methylpropyl)benzeneacetyloxy]-(N-methyl-N-carbamoylmethyl)acetamide

A mixture of ibuprofen (1.03 g, 5 mmole), 2-chloroacetylsarcosinamide (0.82 g, 5 mmole), triethylamine (0.8 ml, 5.7 mmole) and sodium

iodide (100 mg) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 20 h. Water (50 ml) was added and the mixture allowed to stand at 4°C for 5 h. The title compound precipitated was isolated by filtration, washed with water and recrystallized from ethanol-water to give 1.35 g (81%). Mp 100-100.5°C.

EXAMPLE 42

2-[2-[(2,3-Dimethylphenyl)amino]-benzoyloxy]-N,N-dimethylacetamide
A mixture of mefenamic acid (2.41 g, 0.01 mole), 2-chloro-N,N-dimethylacetamide (1.6 g, 0.013 mole), triethylamine (1.6 ml, 0.011 mole) and sodium iodide (0.15 g, 0.001 mole) in N,N-dimethylformamide (10 ml) was stirred at 90°C for 2 h. Water (50 ml) was added and the mixture allowed to stand at 4°C for 5 h. The title compound was isolated by filtration, washed with water and recrystallized from ethanol-water (3.0 g, 92%). Mp 85-86°C.

EXAMPLE 43

2-[1-Methyl-5-(α -methylbenzoyl)-1H-pyrrole-2-acetyloxy]-N,N-dimethylacetamide
A mixture of tolmetin (1.29 g, 5 mmole), 2-chloro-N,N-dimethylacetamide (0.74 g, 6 mmole), triethylamine (0.84 ml, 6 mmole) and sodium iodide (50 mg) in N,N-dimethylformamide (10 ml) was stirred at 90°C for 3 h. Water (50 ml) was added and the mixture extracted with ethyl acetate (75 ml). After washing with an aqueous bicarbonate solution and water the extract was dried and evaporated in vacuo. The residue obtained crystallized upon standing at -20°C and was recrystallized from ethanol-ether to give 1.3 g (76%) of the title compound. Mp 108-109°C.

EXAMPLE 44

2-[(+)-6-Methoxy- α -methyl-2-naphthaleneacetyloxy]-N,N-(di- β -hydroxyethyl)acetamide
The compound was prepared from naproxen and 2-chloro-N,N-(di- β -hydroxyethyl)acetamide by the procedure described in Example 1. The

yield was 60%. Recrystallization from ethyl acetate gave an analytically pure product. Mp 113-114°C.

EXAMPLE 45

5

2-[(+)-6-Methoxy- α -methyl-2-naphthaleneacetyloxy]-(N-methyl-N- β -hydroxyethyl)acetamide

The compound was prepared from naproxen and 2-chloro-(N-methyl-N- β -hydroxyethyl)acetamide by the procedure described in Example 1. The
10 yield was 65%. Recrystallization from ethyl acetate gave an analytically pure product. Mp 109-111°C.

EXAMPLE 46

15 2-(6-Phenylacetamidopenicillanoyloxy)-N,N-diethyl-acetamide

A mixture of benzylpenicillin sodium (1.78 g, 5 mmole), 2-chloro-N,N-diethylacetamide (1.05 g, 7 mmole) and sodium iodide (75 mg) in N,N-dimethylformamide (10 ml) was stirred at room temperature for 18 h. Water (60 ml) was added and mixture extracted with ethyl acetate (2 x
20 50 ml). The extract was washed with 5% aqueous sodium bicarbonate and water. Evaporation of the dried organic phase in vacuo yielded a residue which crystallized from ethanol-water. Mp 60-61°C.

EXAMPLE 47

25

2-(Benzoyloxy)-(N-methyl-N-(N,N-dimethylglycyloxyethyl)acetamide (monofumarate)

A mixture of 2-(benzoyloxy)-(N-methyl-N- β -hydroxyethyl)-acetamide (0.95 g, 4 mmole), N,N-dimethylglycine (0.41 g, 4 mmole), N,N'-dicyclohexylcarbodiimide (0.82 g, 4 mmole) and 4-toluenesulfonic acid (50 mg) in pyridine (10 ml) was stirred at room temperature for 24 h. Methylene chloride (20 ml) was added. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was extracted with
30 20 ml of boiling ethyl acetate and the extract was evaporated. The oily residue obtained was dissolved in ether (20 ml) and a solution of fumaric acid in 2-propanol was added. After standing overnight at
35 4°C the title compound was isolated by filtration in a yield of 59%.

Recrystallization from methanol-ether gave an analytically pure product. Mp 127-127.5°C.

EXAMPLE 48

5 2-(L-4-Hydroxyphenylalanyloxy)-N,N-diethylacetamide hydrochloride

A mixture of N-tert-butoxycarbonyl L-tyrosine (Boc-L-tyrosine) (1.41 g, 5 mmol), 2-chloro-N,N-diethylacetamide (0.68 ml, 5 mmol), triethylamine (0.7 ml, 5 mmol) and sodium iodide (75 mg, 0.5 mmol) in N,N-dimethylformamide (5 ml) was stirred overnight at room temperature. Water (50 ml) was added and the mixture extracted with ethyl acetate (2 x 50 ml). After washing with an aqueous sodium bicarbonate solution and water the combined extracts were dried and evaporated in vacuo. The solid residue was recrystallized from ethyl acetate to give 1.3 g of Boc-L-tyrosine ester of 2-hydroxy-N,N-diethylacetamide, 15 Mp 130-131°C.

This ester was deprotected by stirring 0.5 g in 3 ml of 2.5 M methanolic HCl. After 1 h a clear solution was obtained. The solution was evaporated in vacuo and the oily residue crystallized from ethanol- 20 ether. Mp 164-166°C.

EXAMPLE 49

2-(4-Hydroxybenzoyloxy)-N,N-diethylacetamide

A mixture of 4-hydroxybenzoic acid (1.38 g, 0.01 mol), 2-chloro-N,N-diethylacetamide (1.4 g, 0.01 mol) triethylamine (1.44 ml, 0.01 mol) and sodium iodide (150 mg, 0.001 mol) in N,N-dimethylformamide (6 ml) was stirred at room temperature for 18 h. Water (100 ml) was added and the mixture allowed to stand at 4°C for 5 h. The title compound was isolated by filtration, washed with water and recrystallized from 30 ethanol-water to give 1.8 g. Mp 148-149°C.

EXAMPLE 50

35 2-(trans-4-(Aminomethyl)cyclohexanoyloxy)-N,N-dimethylacetamide hydrochloride

Tranexamic acid (3.0 g, 0.019 mol) was dissolved in 12 ml of thionyl chloride. The solution was kept at room temperature for 30 min. Upon

addition of ether the acid chloride of tranexamic acid as hydrochloride salt precipitated. It was filtered off and dried over P_2O_5 in vacuo, mp 138-139°C.

- 5 The acid chloride (2.10 g, 0.01 mol) was added portionwise and while stirring to a solution of 2-hydroxy-N,N-dimethylacetamide (1.24 g, 0.012 mol) in 10 ml of dioxane. The solution was stirred at 60°C for 1 h and then cooled to 0-4°C. The precipitate formed was filtered off and recrystallized from ethanol to give 1.5 g of the title compound, mp 183-184°C.
- 10

EXAMPLE 51

- 2-[α -Methyl-4-(2-methylpropyl)benzeneacetyloxy]-(N-methyl-N-(N'-morpholinomethylcarbamoyl)methyl)acetamide hydrochloride
- 15 2-[α -Methyl-4-(2-methylpropyl)benzeneacetyloxy]-(N-methyl-N-carbamoylmethyl)acetamide (0.67 g, 2 mmol), prepared as described in Example 49, was dissolved in 2.5 ml of methanol. Morpholine (0.18 g, 2 mmol) and 0.17 ml of 37% aqueous formaldehyde solution were added. The solution was heated on a steam bath for 15 min. and evaporated in vacuo. The oily residue was dissolved in ether (10 ml) and a 2.5 M
- 20 methanolic solution of HCl (1 ml) was added followed by petroleum ether. The mixture was kept overnight at -20°C to allow precipitation of the title compound which was isolated by filtration, mp 154-155°C.

25 EXAMPLES 52-86

By following the procedures of the foregoing examples several more novel esters of the present invention were prepared. The structure of these esters along with their melting points are shown in Table 2.

30

35

TABLE 2 Compounds of Formula I wherein n = 1

Example number	R-COO- is the acyloxy residue of:	R ₁	R ₂	Mp (°C)
5				
52	Naproxen	CH ₃	CH ₃	150-151
53	Naproxen	CH ₃	CH ₂ CONH ₂	179-180
54	Ibuprofen	CH ₃	CH ₃	oil
10	55	Ketoprofen	CH ₃	oil
56	Ketoprofen	C ₂ H ₅	C ₂ H ₅	oil
57	4-Biphenylacetic acid	CH ₃	CH ₂ CONH ₂	174-175
58	Flurbiprofen	CH ₃	CH ₃	74-75
15	59	Flurbiprofen	C ₂ H ₅	60-61
60	Fenbufen	CH ₃	CH ₃	120-121
61	Fenbufen	C ₂ H ₅	C ₂ H ₅	94-95
62	Indomethacin	C ₂ H ₅	C ₂ H ₅	104-105
63	Indomethacin	CH ₃	CH ₂ CH ₂ OH	138-139
20	64	Indomethacin	CH ₂ CH ₂ OH	144-146
65	Tolfenamic acid	CH ₃	CH ₃	106-107
66	Tolfenamic acid	C ₂ H ₅	C ₂ H ₅	114-115
67	Tolfenamic acid	C ₂ H ₅	CH ₂ CH ₂ OH	85-86
68	Tolfenamic acid	CH ₂ CH ₂ OH	CH ₂ CH ₂ OH	176-180
25	69	Diflunisal	CH ₃	96.5-97
70	Diflunisal	C ₂ H ₅	C ₂ H ₅	75-76
71	Mephenamic acid	CH ₃	CH ₂ CH ₂ OH	176-180

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TABLE 2 (continued)

Example number	R-COO-is the acyloxy residue of:	R ₁	R ₂	Mp (°C)
5				
72	L-methyldopa	C ₂ H ₅	C ₂ H ₅	122-124
73	Sulindac	C ₂ H ₃	C ₂ H ₅	100-101
74	Benzylpenicillin	CH ₃	CH ₃	71-72
10	75 Furosemide	CH ₃	CH ₃	193-194
76	Mecillinam	C ₂ H ₅	C ₂ H ₅	120-122
77	Valproic acid	CH ₃	CH ₃	oil
78	Valproic acid	CH ₃	CH ₂ CONH ₂	57-58
79	Salicylic acid	CH ₃	CH ₃	67.5-68
15	80 Salicylic acid	C ₂ H ₅	C ₂ H ₅	73-74.5
81	Acetylsalicylic acid	C ₃ H ₇	C ₃ H ₇	49.5-50.5
82	Acetylsalicylic acid	iC ₃ H ₇	iC ₃ H ₇	108-109
83	Acetylsalicylic acid	CH ₃	CH ₂ COOC ₂ H ₅	47-48
84	Acetylsalicylic acid	CH ₃	CH ₂ CONH ₂	123-124
20	85 Acetylsalicylic acid	C ₆ H ₁₁	C ₆ H ₁₁	133-134
86	Acetylsalicylic acid	morpholine		97-99

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EXAMPLE 87

Preparation of α -chloroacetylsarcosinamide

5 Sarcosinamide hydrochloride was prepared by reacting methylamine with 2-chloroacetamide as described by Marvel et al. (1946). The compound was recrystallized from ethanol. Mp 160-161°C.

10 A solution of chloroacetyl chloride (0.1 mole, 11.3 g) in benzene (40 ml) was added over 30 min to a mixture of sarcosinamide hydrochloride (0.1 mole, 12.45 g) and sodium bicarbonate (0.25 mole, 20.0 g) in 40 ml of water. The mixture was vigorously stirred for 3 h at room temperature. The aqueous phase was acidified with 5 M hydrochloric acid to pH 5 and extracted with ethyl acetate (3 x 400 ml). The combined extracts were dried over anhydrous sodium sulphate and
15 evaporated in vacuo. The solid residue obtained was recrystallized from ethanol-ether to give 8.5 g (52%) of the title compound. Mp 85-86°C.

EXAMPLE 88

20

2-(Acetyloxy)-N,N-dimethylacetamide

A suspension of anhydrous sodium acetate (16.4 g, 0.2 mole) and 2-chloro-N,N-dimethylacetamide (24.3 g, 0.2 mole) in toluene (70 ml) was refluxed for 4 h. After cooling to room temperature the mixture
25 was filtered and the filtrate washed with water (2 x 10 ml), dried and evaporated in vacuo. The solid residue obtained was recrystallized from ether yielding 22.0 g (76%). Mp 52-53°C.

In-vitro cleavage of ester prodrugs

30

Reaction conditions. Solutions of various derivatives of this invention in aqueous buffer solutions or 50-80% human plasma solutions (pH 7.4) were kept at 37°C. The initial concentration of the derivatives was in the range 3×10^{-4} - 10^{-5} M. At various times an aliquot of the solutions was withdrawn and analyzed by HPLC for remaining
35 derivative as well as for parent acid. For the plasma solutions the aliquot withdrawn was deproteinized with methanol, ethanol or

acetonitrile and after centrifugation, the clear supernatant was injected on HPLC.

Analytical method. An HPLC method was used for the determination of the ester derivatives and their parent acids. In this method a reversed-phase LiChrosorb RP-8 column (250 x 4 mm) was eluted at ambient temperature with mixtures of methanol and 0.01 M acetate buffer pH 5.0; methanol and 0.01 M phosphate buffer pH 4.5 or methanol and 0.02 M phosphate buffer pH 3.5. the composition of the eluant was adjusted for each compound in order to provide an appropriate retention time and separation of ester and the corresponding acid. The flow-rate was 0.6 - 1.6 ml/min and the column effluent was monitored spectrophotometrically at an appropriate wavelength. Quantitation of the compounds was done by measurement of the peak heights in relation to those of standards chromatographed under the same conditions.

The various prodrug esters were found to be cleaved quantitatively to the parent acids in human plasma solutions. An example is shown in Fig. 1. The esters of the present invention hydrolyzed surprisingly rapidly in human plasma although the rate of hydrolysis depends greatly on the substituents R_1 and R_2 in Formula I. The half-lives of hydrolysis of various derivatives in 50% human plasma solutions (pH 7.4; 37°C) are given in Table 3. As can be seen from the data the N,N-disubstituted 2-(acyloxy)acetamide esters are particularly rapidly hydrolyzed. Thus, the half-life for the hydrolysis of 2-(benzoyloxy)-N,N-diethylacetamide is less than 3 sec. In pure buffer solution of the same pH (7.4) and at 37°C the half-life of hydrolysis of this compound and the related esters listed in Table 3 was found to be greater than 1,000 h, thus demonstrating the facile enzymatic hydrolysis at conditions similar to those prevailing in vivo.

At initial concentrations of about 10^{-4} M the progress of hydrolysis of some esters followed strict first-order kinetics (examples are shown in Fig. 2), whereas in other cases mixed kinetics was observed. An example of the latter is shown in Fig. 3. As seen from Fig. 3 the rate of hydrolysis initially followed zero-order kinetics and as the substrate depleted, it changed to follow first-order kinetics. This behaviour is typical for enzyme-catalyzed reactions in which the

initial substrate concentration is higher than the Michaelis constant K_m . At low substrate concentrations, i.e. concentrations similar to those prevailing in vivo for prodrug hydrolysis, the enzymatic reaction is first-order with the half-lives referred to in Table 3.

5 Table 4 shows hydrolysis data for esters of various carboxylic acids according to the present invention. The structure of the acyl moiety has an influence on the enzymatic reactivity but in all cases a quite rapid rate of hydrolysis in plasma was observed. By comparing the
10 rates of hydrolysis of the esters of the present invention with those of the corresponding simple methyl or ethyl esters (Table 5) the much more facile enzymatic hydrolysis of the esters disclosed herein is readily apparent.

15 The esters of the present invention were found to be highly stable in acidic media. For example, no hydrolysis, i.e. (< 1%), of 2-(benzoyloxy)-N,N-diethylacetamide was found to take place in 0.01 M HCl solutions kept at 37°C for 3 h.

20 These results show that the esters of the present invention combine a high susceptibility to undergo enzymatic hydrolysis in plasma with a high stability in aqueous solution, e.g. in acidic medium such as gastric juices. In consequence, for example, the esters will remain intact in the gastro-intestinal tract upon oral administration, the release of the free carboxylic acid agent occurring during the ab-
25 sorption process or in the blood following absorption.

Water-solubility and lipophilicity of the ester prodrugs

The partition coefficients (P) for some esters of the present invention were measured at 22°C using the widely-used octanol-water system. Similarly, the solubility of the derivatives in water or aqueous
30 buffer solutions was determined. The values found for log P and the water-solubilities are included in Table 3.

35 The results obtained show that by varying the substituents R_1 and R_2 and n in Formula I it is readily feasible to obtain ester prodrug derivatives with varying and any desirable lipophilicity or water-solubility with retainment of a great lability to enzymatic hydrolysis. Thus, as seen from Table 3, the derivative 2-(benzoyloxy)-N,N-

(di- β -hydroxyethyl)acetamide is soluble in water to an extent of more than 70% w/v although it is a neutral compound with a positive log P value. As a further example, the corresponding ester derivative of naproxen (Example 44) was found to be more than 20-fold more soluble in 0.01 M HCl than parent naproxen.

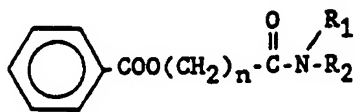
Bioavailability study

The naproxen prodrug derivative described in Example 44 was administered orally to rabbits. Similarly, naproxen itself was given orally to rabbits in an equivalent dose (4.8 mg/kg naproxen). After drug administration, blood samples were taken at various times and the plasma fraction assayed for naproxen and prodrug using an HPLC method at the following conditions: Column: LiChrosorb RP-8; eluent: methanol-0.02 M KH_2PO_4 (pH 3.5) 65:35; detection: UV at 230 nm.

As seen from Table 6 the naproxen prodrug derivative is efficiently absorbed following oral administration. No measurable concentrations ($< 0.1 \mu\text{g/ml}$) of intact naproxen prodrug were observed, thus demonstrating that the prodrug is rapidly converted back to naproxen in vivo in accordance with the "prodrug" definition provided at the outset of this application.

TABLE 3 Rates of enzymatic hydrolysis, water-solubility and partition coefficients for various compounds of the formula

5



$$\text{C}_6\text{H}_5\text{COO}(\text{CH}_2)_n\text{C}(=\text{O})\text{N}(\text{R}_1)\text{R}_2$$

	R ₁	R ₂	n	S ^a (mg/ml)	log P ^b	t _{1/2} ^c (min)
10						
	CH ₃	CH ₃	1	8.8	1.07	0.15
	CH ₃	C ₂ H ₅	1	-	1.27	0.10
	C ₂ H ₅	C ₂ H ₅	1	2.0	2.06	0.04
15	nC ₃ H ₇	nC ₃ H ₇	1	1.1	2.65	0.14
	iC ₃ H ₇	iC ₃ H ₇	1	0.12	2.56	0.08
	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂	1	0.71	2.34	0.08
	nC ₄ H ₉	nC ₄ H ₉	1	0.080	3.91	3.1
	iC ₄ H ₉	iC ₄ H ₉	1	0.081	3.80	<1.5
20	CH ₃	C ₆ H ₁₁	1	0.14	2.99	0.54
	C ₆ H ₁₁	C ₆ H ₁₁	1	0.0034	-	407
	CH ₃	CH ₂ CH ₂ OH	1	19.3	0.58	0.20
	C ₂ H ₅	CH ₂ CH ₂ OH	1	10.8	0.93	0.16
	CH ₂ CH ₂ OH	CH ₂ CH ₂ OH	1	720	0.17	0.42
25	CH ₃	CH ₂ CH ₂ OOC-				
		-CH ₂ N(CH ₃) ₂ ^d	1	>200	-	0.08
	CH ₃	CH ₂ CONH ₂	1	30.2	0.08	0.13
	CH ₃	CH ₂ COOC ₂ H ₅	1	6.0	1.56	0.22
	CH ₃	CH ₃	2	17.6	1.28	5.6
30	CH ₃	CH ₃	3	13.9	1.86	14.1
	CH ₃	CH ₂ CH ₂ N(CH ₃) ₂ ^d	1	>100	-	0.12
	CH ₂ CH ₂ OCH ₃	CH ₂ CH ₂ OCH ₃	1	-	-	0.25

35

TABLE 3 (continued)

	n	S ^a (mg/ml)	log p ^b	t _{1/2} ^c (min)
5				
10				
15				
20				
25				
30				
35				

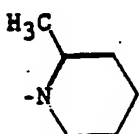
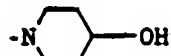
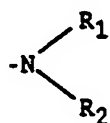
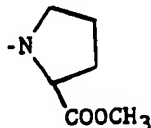
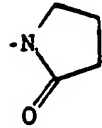
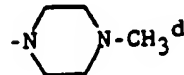


TABLE 3 (continued)

5		n	s ^a (mg/ml)	log P ^b	t _{1/2} ^c (min)
10		1	2.4	1.42	1.9
		1	0.49	1.83	18
15		1	>100	-	12.7

^a Solubility in water at 22°C.

^b P is the partition coefficient between octanol and water at 22°C.

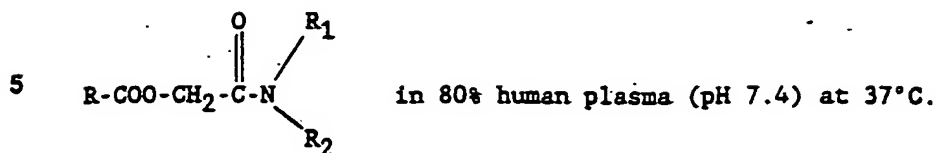
20 ^c Half-life of hydrolysis in 50% human plasma (pH 7.4) at 37°C.

^d Hydrochloride salt

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30

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TABLE 4. Half-lives ($t_{1/2}$) of hydrolysis of various compounds of the formula


10	R-COO- is the acyloxy residue of	R ₁	R ₂	t _{1/2} (min)
15	Naproxen	CH ₃	CH ₃	1.5
		C ₂ H ₅	C ₂ H ₅	0.6
		CH ₂ CH ₂ OH	CH ₂ CH ₂ OH	1.3
		CH ₃	CH ₂ CONH ₂	2.5
20	Ibuprofen	CH ₃	CH ₃	8.6
		CH ₃	CH ₂ CONH ₂	9.6
		CH ₃	CH ₂ CONHCH ₂ N 	10.8
25	Ketoprofen	CH ₃	CH ₃	1.1
		C ₂ H ₅	C ₂ H ₅	0.5
		CH ₃	CH ₂ CONH ₂	2.3
30	Flurbiprofen	CH ₃	CH ₃	10.8
		C ₂ H ₅	C ₂ H ₅	4.7
35	Fenbufen	CH ₃	CH ₃	9.2
		C ₂ H ₅	C ₂ H ₅	3.8
	Indomethacin	CH ₃	CH ₃	130
		C ₂ H ₅	C ₂ H ₅	25
CH ₃		CH ₂ CH ₂ OH	140	
CH ₂ CH ₂ OH		CH ₂ CH ₂ OH	88	
Sulindac	C ₂ H ₅	C ₂ H ₅	26	

TABLE 4 (continued)

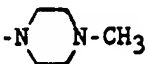
5	R-COO- is the acyloxy residue of	R ₁	R ₂	t _{1/2} (min)
10	Tolmetin	CH ₃	CH ₃	14.6
		C ₂ H ₅	C ₂ H ₅	13.4
	Tolfenamic acid	CH ₃	CH ₃	2.8
15		C ₂ H ₅	C ₂ H ₅	5.0
		C ₂ H ₅	CH ₂ CH ₂ OH	3.0
	4-Aminobenzoic acid	C ₂ H ₅	C ₂ H ₅	0.6
20	Tranexamic acid	CH ₃	CH ₃	1.2
	L-Phenylalanine	C ₂ H ₅	C ₂ H ₅	0.2
	L-Tyrosine	C ₂ H ₅	C ₂ H ₅	0.5
25	4-Hydroxybenzoic acid	C ₂ H ₅	C ₂ H ₅	1.8
	Salicylic acid	CH ₃	CH ₃	0.08
		C ₂ H ₅	C ₂ H ₅	0.08
		CH ₃	CH ₂ CONH ₂	0.33
				22
	Mefenamic acid	CH ₃	CH ₃	2.4
30	Diflunisal	C ₂ H ₅	C ₂ H ₅	79
	4-Biphenylacetic acid	CH ₃	CH ₂ CONH ₂	2.1

TABLE 5. Half-lives ($t_{1/2}$) of hydrolysis of esters of various drugs containing a carboxylic acid function in 80% human plasma ^a

5	Acid	$t_{1/2}$	
		Methyl ester	N,N-diethylglycol-amide ester
10			
	Salicylic acid	17.6 h	0.08 min
	Benzoic acid	2.0 h	0.04 min
	Naproxen	20.1 h ^b	0.6 min
15	Ketoprofen	> 20 h	0.5 min
	Fenbufen	4.7 h	3.8 min
	Tolmetin	19 h	13.4 min
	Tolfenamic acid	100 h	5.0 min
	Indomethacin	150 h	25 min
20	L-Phenylalanine	29 min	0.2 min
	4-Hydroxybenzoic acid	>50 h	1.8 min
	4-Aminobenzoic acid	>100 h ^b	0.6 min
	Tranexamic acid	>3 h	1.2 min ^c
	L-Tyrosine	59 min ^b	0.5 min
25			

^a At pH 7.4 and 37°C.

^b Value for ethyl ester

^c Value for N,N-dimethylglycolamide ester

30

35

TABLE 6. Plasma concentrations of naproxen following oral administration of naproxen (4.8 mg/kg) or the equivalent amount of the N,N-(β -hydroxyethyl)glycolamide ester of naproxen to rabbits.

5

		Naproxen plasma conc.	
Time after administration		(ug/ml)	
	(min)	After naproxen administration	After ester administration
10	10	2.8	2.7
	25	5.1	5.7
	50	6.4	8.3
	75	7.1	8.2
	100	7.4	7.7
15	125	7.1	6.7
	200	5.4	4.0
	300	3.6	3.6
	400	2.7	3.3
	450	2.4	3.2

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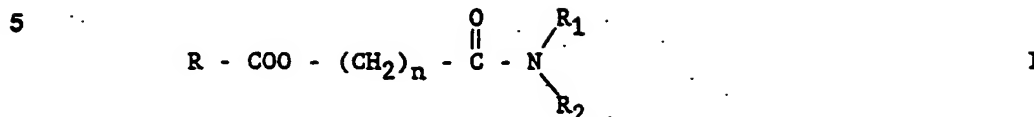
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CLAIMS

1. Compounds of the formula I



10 wherein R-COO- represents the acyloxy residue of a carboxylic acid drug or medicament,

n is an integer from 1 to 3, and

15 R₁ and R₂ are the same or different and are selected from a group consisting of an alkyl group, an alkenyl group, an aryl group, an aralkyl group, a cycloalkyl group, in which the alkyl, alkenyl, aryl, aralkyl or cycloalkyl group is unsubstituted or substituted with one or more substituents selected from:

- 20
- a halogen atom,
 - a hydroxy group,
 - a carbonyl group,
 - a straight or branched-chain alkoxy group having the formula R₃-O-, wherein R₃ represents an alkyl group or an aryl group, which groups may be unsubstituted or substituted with one or more of a halogen atom or a hydroxy group,
 - 25 - a carbamoyl group having the formula $-\text{CON} \begin{matrix} \nearrow \text{R}_5 \\ \searrow \text{R}_4 \end{matrix}$,

30 wherein R₄ and R₅ are the same or different and are hydrogen, an alkyl group or are selected from a group having the formula -CH₂NR₆R₇, wherein R₆ and R₇ are the same or different and are hydrogen, an alkyl group, or together with the adjacent nitrogen atom form a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from the group consisting of

35 nitrogen, oxygen, and sulfur,

- an amino group having the formula -NR₈R₉, wherein R₈ and R₉ are the same or different and are hydrogen, an alkyl group or

together with the adjacent nitrogen atom form a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur,

5

- an acyloxy group having the formula $-COOR_{10}$, wherein R_{10} is an alkyl, aryl or aralkyl group,

10

- an oxyacyl group having the formula $R_{11}COO-$ wherein R_{11} is hydrogen, an alkyl group, an aryl group, an aralkyl group, a cycloalkyl group, in which the alkyl, aryl, aralkyl or cycloalkyl group is unsubstituted or substituted with one or more of a halogen atom, a hydroxy group, an alkoxy group of the formula R_3-O- as defined above, a carbamoyl group of the formula $-CONR_4R_5$ as defined above or an amino group having the formula $-NR_8R_9$ as defined above;

15

or R_1 and R_2 are combined so that $-NR_1R_2$ forms a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and which heterocyclic ring may be substituted with a hydroxy group, a carbonyl group, an alkyl group or an oxyacyl group having the formula $R_{11}COO-$, wherein R_{11} is as defined above, or an acyloxy group of the formula $-COOR_{10}$, wherein R_{10} is as defined above;

20

and nontoxic pharmaceutically acceptable acid addition salts thereof with the proviso that if $R_1 = \text{alkyl}$ then $R_2 = \text{alkyl}$, and if $R_1 = CH_2CH_2OH$ then $R_2 = CH_2CH_2OH$.

25

2. Compounds according to claim 1 wherein R-COO is derived from a compound selected from

30

Acetylsalicylic acid
Salicylic acid
Sulindac
Indomethacin
Naproxen

35

	Ibuprofen
	Ketoprofen
	Diflunisal
	Tolmetin
5	Flurbiprofen
	Mefenamic acid
	Tolfenamic acid
	Cefmetazole
	Cefazolin
10	Cephalexin
	Cefaclor
	Cefuroxime
	Cefamandole
	Cefoxitin
15	Benzylopenicillin
	Phenoxyphenylpenicillin
	Ampicillin
	Amoxycillin
	Carbenicillin
20	Azlocillin
	Piperacillin
	6 α -Fluoro-11 β -hydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
	9 α -Fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
25	9 α -Fluoro-11 β ,17 α -dihydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
	11 β ,17 α -Dihydroxy-3,20-dioxopregn-4-en-21-oic acid
	9 α -Fluoro-11 β ,16 α ,17 α -trihydroxy-3,20-dioxopregna-4-dien-21-oic acid
30	11 β ,17 α -Dihydroxy-3,20-dioxopregna-1,4-dien-21-oic acid.
	Prostaglandin E ₂
	Prostaglandin F _{2α}
	Prostaglandin E ₁
35	Prostacyclin
	(15R)-15-Methylprostaglandin E ₂ (Arbaprostil)
	Nileprost

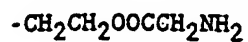
- Ciprostone
 Enalaprilic acid
 Captopril
 N-Cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-
 5 -2-methyl-1-oxopropyl]glycine
 1-[4-Carboxy-2-methyl-2R,4R-pentanoyl]-2,3-dihydro-
 -2S-indole-2-carboxylic acid
 [2S-[1[R*(R*)]],2 α ,3 α ,7 α]-1-[2-[[1-carboxy-3-phenyl-
 propyl]amino]-1-oxopropyl]octahydro-1H-indole-2-
 10 carboxylic acid
 5-Aminosalicylic acid
 Methyldopa
 L-Dopa
 Valproic acid
 15 Tranexamic acid
 Furosemide
 Methotrexate
 Chlorambucil
 Clofibric acid
 20 Amphotericin B
 6-Aminocaproic acid
 Mecillinam
 Tretinoin
 4-Aminomethylbenzoic acid
 25 Mycophenolic acid and
 D,L-2,4-Dihydroxyphenylalanine

3. Compounds according to claim 1 or 2 wherein n is 1.

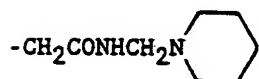
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4. Compounds according to claim 2 wherein n is 1, R₁ is methyl or ethyl, and R₂ is selected from

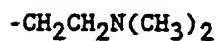
- CH₂CH₂OH
 -CH₂CONH₂
 35 -CH₂CH₂CONH₂
 -CH₂CH₂OOCCH₂N(CH₃)₂



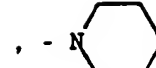
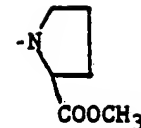
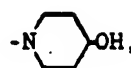
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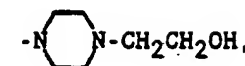
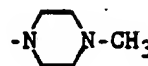
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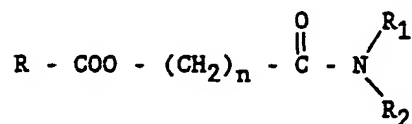
or $-\text{NR}_1\text{R}_2$ is

20



5. Compounds of the formula I

25



I

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wherein n is an integer from 1 to 3, R_1 and R_2 both are alkyl or both are $-\text{CH}_2\text{CH}_2\text{OH}$ and $\text{R}-\text{COO}$ is the acyloxy residue of one of the following carboxylic acid drugs:

Salicylic acid

Sulindac

Indomethacin

35

Naproxen

Ibuprofen

Ketoprofen

	DiFlunisal
	Tolmetin
	Flurbiprofen
	Mefenamic acid
5	Tolfenamic acid
	Cefmetazole
	Cefazolin
	Cephalexin
	Cefaclor
10	Cefuroxime
	Cefamandole
	Cefoxitin
	Benzylpenicillin
	Phenoxymethylpenicillin
15	Ampicillin
	Amoxycillin
	Carbenicillin
	Azlocillin
	Piperacillin
20	6 α -Fluoro-11 β -hydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
	9 α -Fluoro-11 β ,17 α -dihydroxy-16 β -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
	9 α -Fluoro-11 β ,17 α -dihydroxy-16 α -methyl-3,20-dioxopregna-1,4-dien-21-oic acid
25	11 β ,17 α -Dihydroxy-3,20-dioxopregn-4-en-21-oic acid
	9 α -Fluoro-11 β ,16 α ,17 α -trihydroxy-3,20-dioxopregna-4-dien-21-oic acid
	11 β ,17 α -Dihydroxy-3,20-dioxopregna-1,4-dien-21-oic acid.
30	Prostaglandin E ₂
	Prostaglandin F _{2α}
	Prostaglandin E ₁
	Prostacyclin
	(15R)-15-Methylprostaglandin E ₂ (Arbaprostil)
35	Nileprost
	Ciprostene
	Enalaprilic acid

Captopril

N-Cyclopentyl-N-[3-[(2,2-dimethyl-1-oxopropyl)thio]-

-2-methyl-1-oxopropyl]glycine

1-[4-Carboxy-2-methyl-2R,4R-pentanoyl]-2,3-dihydro-

5 -2S-indole-2-carboxylic acid

[2S-[1[R*(R*)]],2 α ,3 α ,7 α]-1-[2-[[1-carboxy-3-phenyl-

propyl]amino]-1-oxopropyl]octahydro-1H-indole-2-

carboxylic acid

5-Aminosalicylic acid

10 Methyl dopa

L-Dopa

Valproic acid

Tranexamic acid

Furosemide

15 Methotrexate

Chlorambucil

Clofibril acid

Amphotericin B

6-Aminocaproic acid

20 Mecillinam

Tretinoin

4-Aminomethylbenzoic acid

Mycophenolic acid and

D,L-2,4-Dihydroxyphenylalanine

25

6. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a pharmaceutically effective amount of a compound according to any of claims 1-5.

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7. A process for preparing a compound of the formula I as defined in claim 1 or 5 comprising

a) reacting the carboxylic acid agent of the formula A or a salt thereof

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R-COOH

(A)

wherein R-COO- is defined as above in connection with formula I, with a compound having the formula B:



10 wherein n, R₁ and R₂ are as defined above and X is a suitable leaving group; or

b) reacting a compound of the formula B, wherein X is hydroxy, with an acid of the formula A or with the corresponding acid chloride of the formula C

15



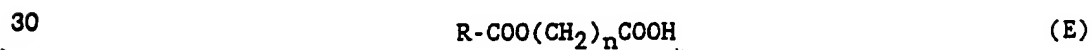
or

20 reacting a compound of the formula D



25

wherein R₁ and R₂ are as defined above in connection with formula I, with an acid of the formula E



wherein R-COO- and n are as defined above in connection with formula I, or with the corresponding acid chloride (or acid anhydride) of the formula F

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(F)

8. The use of a compound according to any of claims 1-5 for preparing a pharmaceutical composition for use in therapy.

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1/3

Fig. 1.

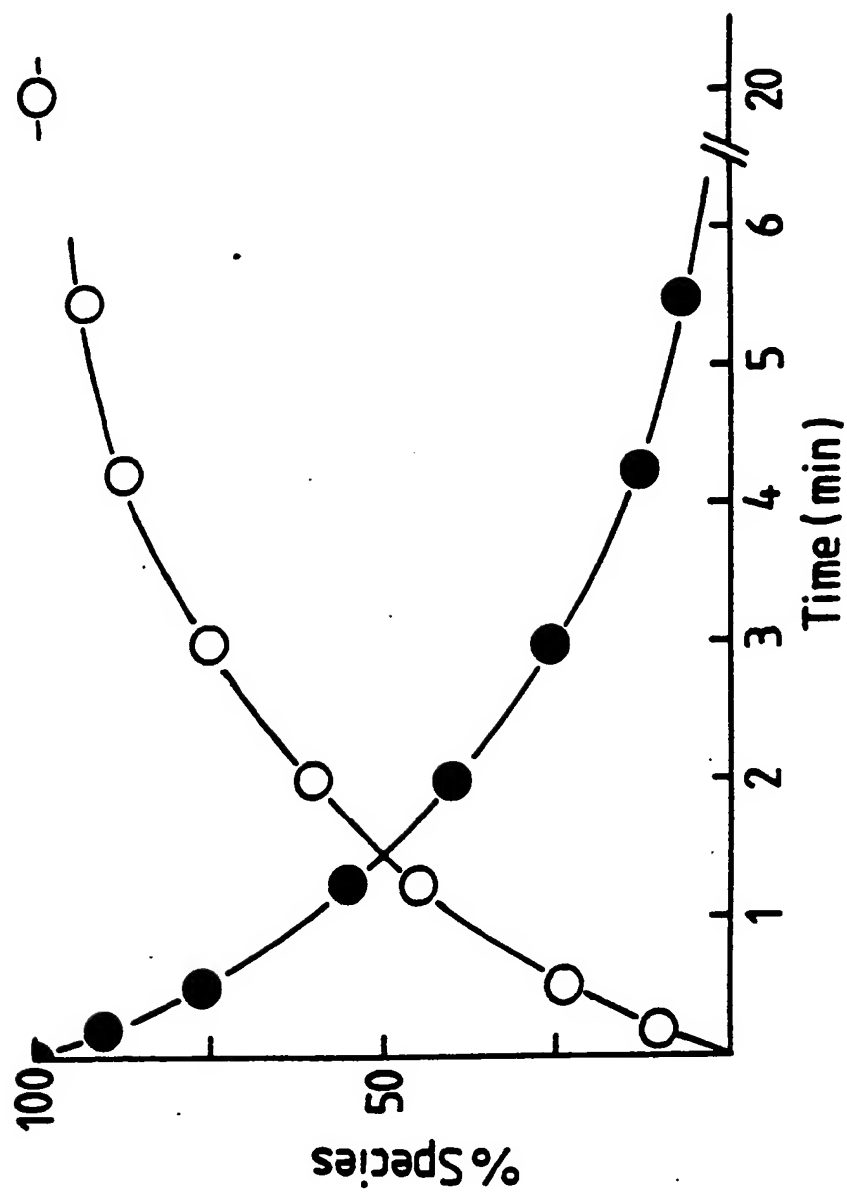


Fig. 2.

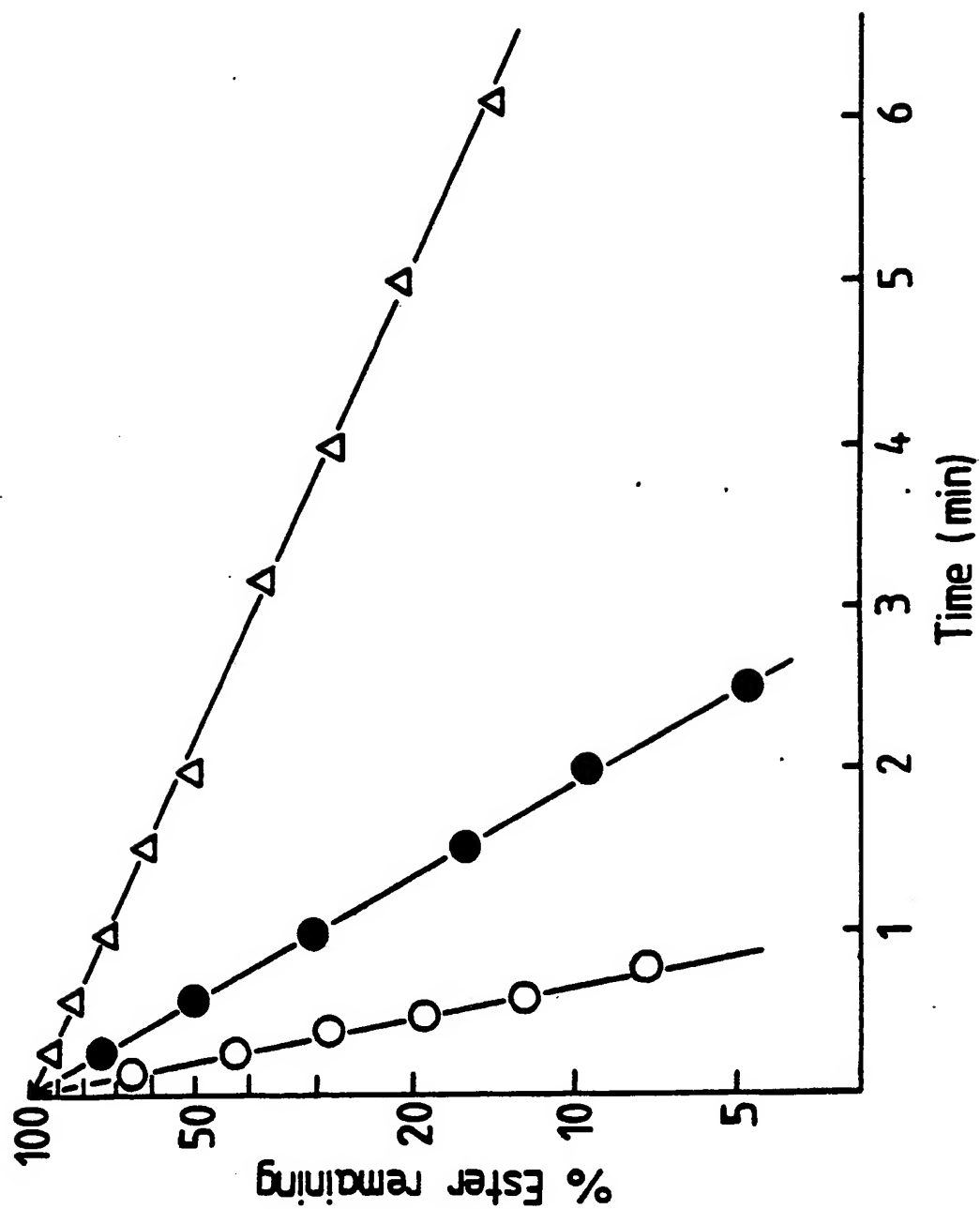
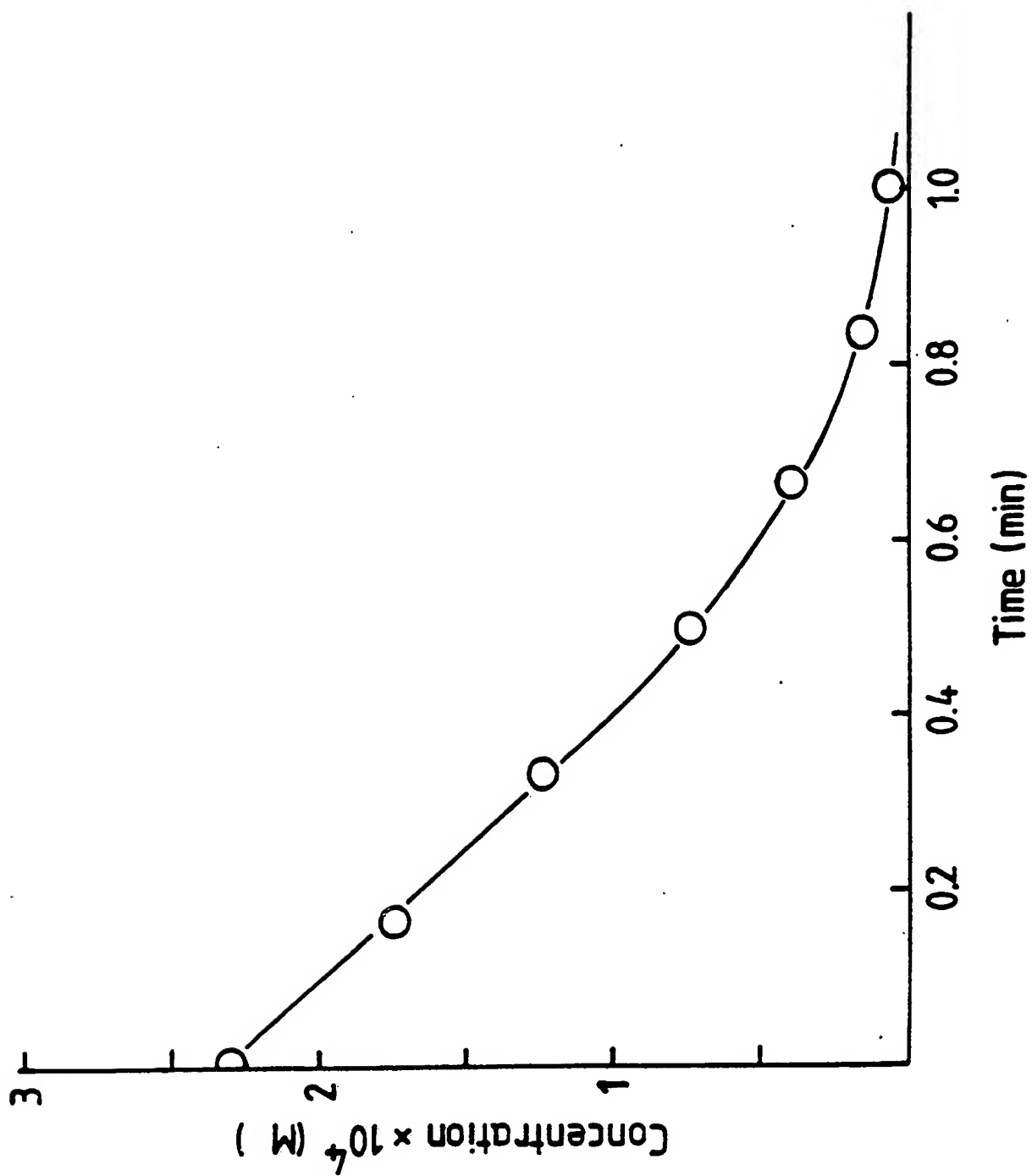


Fig. 3.



INTERNATIONAL SEARCH REPORT

PCT/DK87/00104

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC 4 C 07 C 103/30, A 61 K		
II. FIELDS SEARCHED		
Minimum Documentation Searched 7		
Classification System	Classification Symbols	
IPC 4 US C1	C 07 C 69/00, /003, 103/00, /30; A 61 K 31/21, /215 514:514, 529, 613	
Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched *		
SE, NO, DK, FI classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT 8		
Category *	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No. 13
A	EP, A, 0 227 355 (THE UNIVERSITY OF KANSAS) 1 July 1987	
A	EP, A, 0 106 541 (BUNDGAARD H ET AL) 25 April 1984	
A	WO, A, 86/00066 (CIBA-GEIGY AG) 3 January 1986	
A	EP, A, 0 224 178 (BAYER AG) 3 June 1987 See page 2-3	
A	US, A, 4 678 806 (BALDWIN ET AL) 7 July 1987 See column 1	
A	EP, A, 0 237 051 (FUJISAWA PHARMACEUTICAL CO, LTD) 16 September 1987	
.../...		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents: 10</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
1987-12-10	1987-12-17	
International Searching Authority	Signature of Authorized Officer	
Swedish Patent Office	 Solveig Gustavsson	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

partially,

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers _____, because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim numbers 1-8, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
because R covers a large number of different chemical compounds.

3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category*	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 4 206 220 (SLOAN) 3 June 1980	
A	US, A, 4 235 887 (VOORHEES ET AL) 25 November 1980 See column 3	
A	EP, A, 0 073 397 (MILES LABORATORIES INC) 9 March 1983 See claim 1	
X	US, A, 4 588 525 (ARNOLD, JR ET AL) 13 May 1986 See claim 12.	1-8
A	EP, A, 0 201 829 (BAYER AG) 20 November 1986	
X	CH, A, 513 815 (UGINE KUHLMANN) 15 October 1971 & NL, 6910436 DE, 1935344 GB, 1230673 FR, M, 7487 CH, 506472 BE, 734487 US, 3792082	1-8
X	EP, A, 0 077 720 (PIERRE FABRE S.A.) 27 April 1983 & FR, 2514355 JP, 58077849 AT, E, 8618 US, 4510142	1-8
X, P	Chemical Abstracts, Vol 106 (1987) abstract No 78187t, 16 March 1987	1-8